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GASTROENTEROLOGY 13:4 (Oct.) 1949[1]
Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared, in such conditions as the syndrome of irritable bowel associated with either constipation or diarrhea, intestinal stomas and the milder forms of intestinal infections associated with diarrhea. It is of little value in the severe forms of diarrhea, that of extensive ulcerative
possibly be
rapid to all
N. Y. STATE J. MED. 48:16 (Aug.) 1948[2]
Methylcellulose in dosages of 1 to 6 Gm. daily proved effective for the relief of chronic or acute constipation in the majority of the 37 cases. Its use resulted in the passage of a normal, soft, bulky stool without griping, cramping, or tenesmus in most cases. Its prolonged use (up
not produce evidence
months) did
or toxicity.
GERIATRICS 6:5 (Oct.) 1951[3]
A further observation indicated that when stimulant laxatives are taken, diarrhea, that is, loose watery stools, result. In those cases benefited by bulk laxatives, as Cellothyl, this did not occur, and was considered by us to be of considerable value. Frequently geriatric patients take laxatives causing diarrhea and then seek medication for control.
medication is ordered with resulting intermittent diarrhea
Furthermore, diarrhea in the aged should not
AM. J. DIGEST. DIS. 18:9 (Sept.) 1951[4]
1. In a series of 37 pediatric patients with bowel dysfunction, including constipation, diarrhea, and irritable bowel syndrome, methylcellulose was a helpful adjunct to general management.
2. A good response was obtained in 34 of the cases and in most instances, it was possible to discontinue medication after a reasonable period
N. Y. STATE J. MED. 52:1 (Jan.) 1952[5]
ories likewise responded to Cellothyl with a daily bowel movement of normal consistency. In three cases which required severe laxatives or periodic high enemas, there were established with Cellothyl daily evacuations of formed stools. Although no improve-
PERMANENTE FOUND. M. BULL. 7:2 (July) 1949
A preliminary report is given on the therapeutic effectiveness of methylcellulose in the management of chronic constipation. The material was of beneficial effect in most patients suffering from rectal constipation and in a large number of patients suffering from constipation due to spasticity of the colon. Atony of the bowel apparently required more stimulation than
J. OKLAHOMA M. A. 43:360 (Aug.) 1950[7]
Methylcellulose was effective when used in either spastic or atonic constipation, in patients of all builds, in all age groups and in both males and females. It provided a useful adjunct in the therapy of mucous colitis, diverticulosis, chronic diarrhea, diarrhea alternating with constipation, constipation associated with peptic ulcer and gall bladder disease, functional cardiac states and many forms of neuras-

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Bibliography: 1. Bargen, J. A. 2. Schweig, K. 3. Wechsler, L.; Kessler, L. A., and Goldsmith, M. F. 4. Keeler, K. C., and Rusk, H. A. 5. Seidmon, E. E. P. 6. Newey, J. A., and Goetzl, F. R. 7. Musick, V. H.

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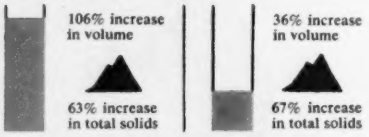

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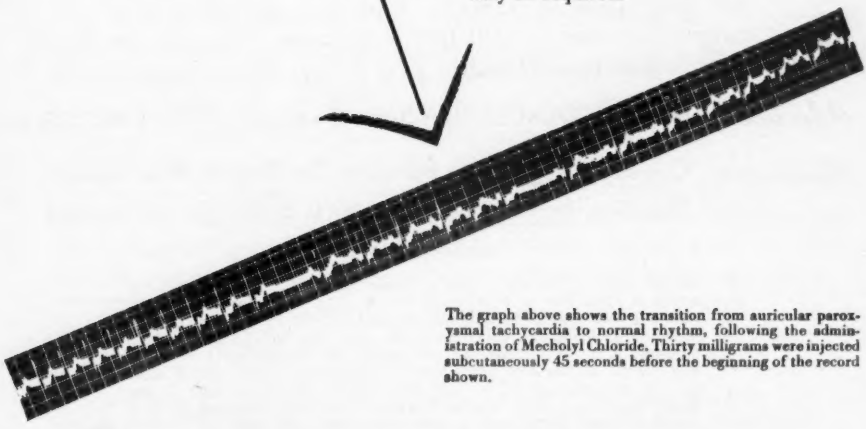

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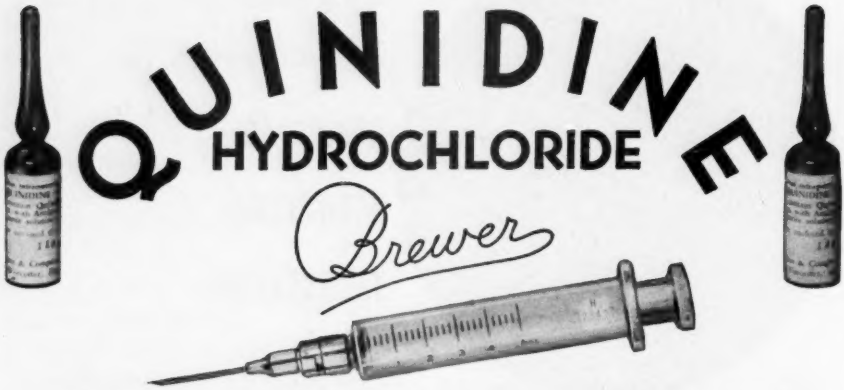

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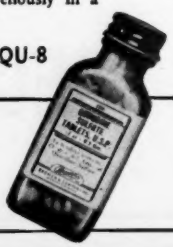

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Editorials

VECTORCARDIOGRAPHY

THE VECTORCARDIOGRAM is a record of the time course of the mean instantaneous electric vectors produced by auricular and ventricular depolarization and repolarization. The principle of vectorcardiography was advanced by Mann in 1920, when he described the method for manually constructing the *monocardiogram* from the standard leads of the electrocardiogram.[1] He later constructed a special three-coil galvanometer for automatically recording the trace directly from man.[2] Wilson and Johnston[3] in 1938, Schellong and associates[4] in 1937, and Hollmann and Hollmann[5] in 1938 independently applied the cathode-ray oscilloscope to record the vectorcardiogram. Because the oscilloscope, with its suitable amplifiers, is one of the best recorders available today for tracing accurately the electrical events from the heart, it has supplanted other recorders[6] and the tedious process of drawing the vectorcardiogram manually from the electrocardiogram.

Except for the excellent advancements in theory and recording by Wilson and Johnston, Schellong, and Hollmann and Hollmann and the appearance of other sporadic papers, there was little interest in vectorcardiography for about 20 years after Mann's publication. Wilson and associates[7] then introduced the concept of spatial vectorcardiography and the equilateral tetrahedral reference frame at about the same time that others[8] were becoming interested in the spatial orientation of

1. Mann, H.: A Method of Analyzing the Electrocardiogram, Arch. Int. Med. **25**:283, 1920.

2. Mann, H.: The Monocardiograph, Am. Heart J. **15**:681, 1938.

3. Wilson, F. N., and Johnston, F. D.: The Vectorcardiogram, Am. Heart J. **16**:14, 1938.

4. Schellong, F.; Heller, S., and Schwingel, E.: Das Vektordiagramm: Eine Untersuchungsmethode des Herzens, Ztschr. Kreislaufforsch. **29**:497 and 596, 1937. Schellong, F.: Grundzüge einer klinischen Vektordiagraphie des Herzens, Berlin, Springer-Verlag, 1939.

5. Hollmann, H. E., and Hollmann, W.: Das Einthovensche Dreiecksschema als Grundlage neuer elektrokardiographischer Registriermethoden, Ztschr. klin. Med. **134**:732, 1938.

6. Mann.[2] Shillingford, J., and Brigden, W.: The Vectorcardiogram in 100 Healthy Subjects Using a New Drawing Instrument, Brit. Heart J. **13**:233, 1951.

7. Wilson, F. N.; Johnston, F. D., and Kossmann, C. E.: The Substitution of a Tetrahedron for the Einthoven Triangle, Am. Heart J. **33**:594, 1947.

8. (a) Duchosal, P. W.; Grosgurin, J., and Sulzer, R.: Étude des relations entre le vectocardiogramme et les dérivations standard, unipolaires des membres et précordiales, Acta cardiol. **3**:273, 1948. (*b*) Duchosal, P. W., and Sulzer, R.: La vectocardiographie, Basel, S. Karger, 1949.

the vector forces and the spatial vectorcardiogram. Within the past five years interest in this problem has mounted the world over.[9]

As would be expected with any relatively new field into which enter many persons of various levels of interest and training, numerous problems and controversies have developed. Some are sufficiently important to merit early clarification, whereas others are not of such great moment and will receive solution in due time. Some of these problems involve philosophic points of view, others biased opinions or a tendency to advance too rapidly the general application of vectorcardiography to clinical cardiology, and still others the desire to encourage general acceptance of methods and views in the field before these have been adequately evaluated and found to be satisfactory.

Existing important problems include need for standardization of (1) the planar and spatial reference system without hampering research, (2) nomenclature, (3) electrode positions as well as polarity of the electrodes, and (4) minimal requirements of the recorders. Such problems must be solved fairly soon in order to permit comparison of vectorcardiographic data obtained by various investigators. Decisions must be made in the best interest of the field of vectorcardiography and without personal prejudice. Foremost, the solutions must be reached in such a manner and at such a time as not to hamper investigation in the subject. The opinions of investigators themselves must, of course, be sought in order to obtain the most satisfactory solutions. Obviously, if vectorcardiography is to have clinical applications the most adequate and simplest methods and nomenclature must be adopted for general use.

It is well to dispel any fears among clinicians or investigators who are not directly involved in vectorcardiography that the planar or spatial vectorcardiogram now provides additional practical clinical information not already available in conventional standard and precordial electrocardiograms. Furthermore, in its

9. (*a*) Duchosal and Sulzer.[8b] (*b*) Vastesaeger, M. M., and Rochet, J.: La stéréovectocardiographie et la stéréovectocardioscopie: Methodes cliniques d'étude de la répartition spatiale des potentiels cardiaques, Trav. lab. Inst. Solvay phys. **29**:40, 1944; (*c*) Les propriétés du vectocardiogramme spatial de l'homme normal et ses variations physiologiques, ibid. **29**:55, 1944. (*d*) Conway, J. P.; Cronvich, J. A., and Burch, G. E.: Observations on the Spatial Vectorcardiogram in Man, Am. Heart J. **38**:537, 1949. (*e*) Abildskov, J. A.; Burch, G. E., and Cronvich, J. A.: The Validity of the Equilateral Tetrahedron as a Spatial Reference System, Circulation **2**:122, 1950. (*f*) Abildskov, J. A.; Jackson, C. E.; Burch, G. E., and Cronvich, J. A.: The Spatial Vectorcardiogram in Right Bundle Branch Block, ibid. **3**:600, 1951. (*g*) Arrighi, F. P.: El eje eléctrico del corazón en el espacio, con el estudio, y empleo de las derivaciones sagitales: Eje eléctrico y electrocardiograma en el plano sagital, Prensa med. argent. **26**:253, 1939. (*h*) Cronvich, J. A.; Conway, J. P., and Burch, G. E.: Standardizing Factors in Electrocardiography, Circulation **2**:111, 1950. (*i*) Den Boer, W.: Vectorcardiographie, Utrecht, Drukkerij, 1951. (*j*) Hollmann, W., and Guckes, E.: Das Triogramm und seine klinische Bedeutung, Arch. Kreislaufforsch. **4**:69, 1939. (*k*) Jouve, A.; Buisson, P.; Albouy, A.; Velasque, P., and Bergier, G.: La vectocardiographie en clinique, Paris, Masson & Cie, 1950. (*l*) Grishman, Arthur, and Scherlis, Leonard: Spatial Vectorcardiography, Philadelphia, W. B. Saunders Co., 1952. (*m*) Pantridge, J. F.; Abildskov, J. A.; Burch, G. E., and Cronvich, J. A.: A Study of the Spatial Vectorcardiogram in Left Bundle Branch Block, Circulation **1**:893 (April, Pt. 2), 1950. (*n*) Rochet, J., and Vastesaeger, M. M.: Relief vrai et faux relief en stereovectocardiographie, Compt. rend. Soc. biol. **138**:992, 1944. (*o*) Milnor, W. R.; Genecin, A.; Talbot, S. A., and Newman, E. V.: A Vectorcardiographic Study of the "Q_3" Deflection in Cases of Myocardial Infarction and in Normal Subjects, Bull. Johns Hopkins Hosp. **89**:281, 1951.

current status of development, it should not replace electrocardiography. The electrocardiogram and the vectorcardiogram present the same electrical events from the heart, and both provide essentially the same information. The same inescapable difficulties, such as (1) lack of remoteness of the electrode positions, (2) nonhomogeneity of conducting medium, and (3) lack of a point source of current, are common to both vectorcardiography and electrocardiography. It is the hope of those interested in spatial vectorcardiography, however, that the latter may yield supplementary information not procurable from the electrocardiogram, but such pertinent data of clinical value have not yet been discovered despite contentions to the contrary by some investigators. From the clinical point of view, it would seem unwise to add the vectorcardiogram to the already complex armamentarium of the clinician if it cannot furnish additional aid in diagnosis and treatment of cardiac problems.

The spatial vectorcardiogram is a record of the time course of the mean spatially oriented instantaneous electric vectors produced by the process of auricular and ventricular depolarization and repolarization. The oscilloscopically recorded trace presents these mean spatial vectors in detail without tedious manual drawing and in a fashion to permit direct visualization and consideration. Even though the electrocardiogram provides the same data, its manner of being recorded and conventional interpretation usually preclude, or at least do not generally encourage, consideration of spatial vector forces when it is studied and interpreted. Since the spatial vector forces are presented as such in the vectorcardiogram, the record is considered primarily in terms of the spatial vector quantities. It follows, therefore, that the results of investigations published to date are concerned with a description of the variations of these mean instantaneous spatial vectors with time, a problem which has been neglected in electrocardiography.

The vectorcardiogram, because of certain shortcomings, is unlikely to displace the electrocardiogram in the near future. The most important of its disadvantages is its failure to record satisfactorily temporal phenomena—even for the loops themselves. A trace which does not record adequately P-R intervals, Q-T intervals, P-R segment durations, irregularities in cardiac rhythm, or even simply cardiac rate, cannot replace, but can only supplement, the electrocardiogram. True, the spatial vectorcardiogram, especially the stereoscopically recorded spatial vectorcardiogram of a single cardiac cycle, presents more details of the magnitude and direction of the spatial vector forces associated with the electrical events of the cardiac cycle than do conventionally recorded standard leads and special leads of the electrocardiogram. However, with the wealth of experience and information already available in electrocardiography, the latter continues to be the record of choice in clinical medicine, whereas the vectorcardiogram remains the experimental method yet to establish its clinical role.

It is important to realize that the spatial vectorcardiogram cannot be derived accurately from the conventional precordial leads any more than the precordial leads can be obtained accurately from the vectorcardiogram. This is not possible because the precordial electrode is placed so near the heart for recording the precordial leads

that it is semidirect and not remote, as indicated by Wilson and his associates. In fact, this characteristic of the precordial electrode is exploited to localize lesions of the heart more sharply.

It is obviously no more possible to describe the spatial vectorcardiogram and its variations in such brief space than it would be to describe the electrocardiogram with all its variations. Furthermore, a description of the normal and abnormal records obtained with the equilateral tetrahedral reference frame used in our laboratory may be of little value to those employing other reference frames. Examples of the spatial vectorcardiogram and of the trace of its planar projections may be obtained from the literature and available monographs [10] on the subject.

Spatial vectorcardiography is an interesting and intriguing subject which must still be relegated to research medicine and not to clinical medicine. Many important problems remain to be solved. Certainly, research in the field should be supported and encouraged, but the use of the vectorcardiogram in clinical medicine for a service fee or with the contention of elucidating a clinical problem which cannot be clarified by proper use and interpretation of conventional electrocardiograms is to be discouraged. It is well to realize that the need in clinical electrocardiography today is not for another even more complex record but rather for proper recording, application, and interpretation in electrocardiography.

G. E. Burch, M.D.

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10. Duchosal and Sulzer.[8b] Footnote 9*i* and *k*. Donzelot, E.; Milovanovich, J. B., and Kaufmann, H.: Études pratiques de vectographie, Paris, L'Expansion scientifique française, 1950. Grishman, A., and Scherlis, L.: Spatial Vectorcardiography, Philadelphia, W. B. Saunders Company, 1952.

THE LIVER IN OBESITY

SAMUEL ZELMAN, M.D.
TOPEKA, KAN.

EXPERIMENTAL obesity produced by hypothalamic injury in various species of animals is uniformly accompanied with liver damage, progressing occasionally to cirrhosis.[1] In hereditarily obese strains of mice, liver damage is also seen uniformly, and even tumors of the liver are observed.[2] Although the increased incidence in human obesity of gall-bladder disease [3] and diabetes mellitus [4] has long been known, and although these conditions may lead independently to liver disease, there does not appear to be in the literature a consideration of the existence of liver damage in obesity per se.

The majority of obese persons show a significant decrease in carbohydrate tolerance,[5] and this impairment has been related to the duration rather than to the degree of obesity.[6] Similar decreases in carbohydrate tolerance are observed in the experimental obesity of hypothalamic injury [1] and in hereditarily obese mice.[7] Newburgh and Conn [8] suggested that the disturbed carbohydrate metabolism occurring with obesity is related to hepatic dysfunction associated with fatty infiltration

From the Medical Service, Winter Veterans Administration Hospital.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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of the liver. They showed that more than 90% of obese hyperglycemic patients became normal with weight reduction, and that return of obesity was associated with return of reduced dextrose tolerance. The diminished carbohydrate tolerance associated with parenchymatous liver damage reflects delayed glycogenetic function of the liver.[9] It may be accompanied, if liver damage is severer, with fasting hypoglycemia due to delayed glycogenolysis and glyconeogenesis as well. These disturbances disappear when the underlying hepatic disease is successfully treated.[10]

That liver disease may be associated with obesity, even in the absence of biliary tract disease, is suggested not only by the reduced carbohydrate tolerance so often found but also by the frequency of digestive disturbances in the obese and by the increased mortality from cirrhosis of the liver found in follow-up studies of subjects overweight at time of issuance of life insurance (see Comment). The present report documents a systematic study of the functional and structural status of the liver in 20 obese men carefully screened to exclude those with any evidence of past or present illness which might affect the liver, other than obesity.

METHODS

Selection of Patients.—Hospitalized obese men were selected who were willing to cooperate in this study, who were at least 50% overweight in terms of ideal standards,[11] and who had no illness involving or likely to involve the liver or any past history of jaundice or of hepatic or biliary disease. Gall-bladder visualizations by the Graham-Cole roentgen contrast method were normal in all subjects selected, any person without proper visualization being rejected, as well as any person revealing gallstones. Diabetic patients requiring insulin were rejected, and those accepted with impaired carbohydrate tolerance were aglycosuric while on the reducing diet. The selected subjects were required to show normal renal function, normal results on routine blood studies, and negative serologic tests, no evidence of disease of the digestive tract, normal basal metabolic rate whenever metabolic status was in question, and no evidence of infection or congestive heart failure. Patients showing histologic evidence of hepatic cirrhosis were rejected for this series, even though they might otherwise have proved acceptable. In the light of the results of this study, the changes in such persons may well have represented end-stages of the hepatic damage of obesity. Amputees were rejected because of the difficulty in estimating their degree of overweight and the unknown effect upon the liver of the absent metabolic requirements and activities of the missing members.

Causes for hospitalization of these persons included psychoneurosis, osteoarthritis, arteriosclerosis and hypertension, vague digestive distress with no objective findings on gastrointestinal studies, hernia, obesity, various unconfirmed admission diagnoses, including those of metabolic or endocrine disease, and participation in this study per se.

Methods of Study.—In addition to routine roentgen studies of the chest and gall bladder, and any other studies specifically indicated for each patient, all were subjected to the gas contrast method of roentgen visualization of the liver and spleen described elsewhere.[12]

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Laboratory determinations for the purpose of this study were in addition to routine hospital determinations and those specifically designed to evaluate each patient's illness. Included were a five-hour oral dextrose-tolerance test, sulfobromophthalein (bromsulphalein®) retention at 45 minutes after injection of 5 mg. per kilogram of body weight, the total serum bilirubin and its one-minute direct-reacting fraction (Watson-Ducci), the serum alkaline phosphatase[4] (Bodansky), the cephalin-cholesterol flocculation (Hanger) and thymol turbidity (Maclagan), serum albumin and globulin (Hôwe), the serum cholesterol and its esterified fraction (Schoenheimer-Sperry), the prothrombin time (Quick), and three urinary urobilinogen determinations (two-hour semiquantitative Ehrlich reaction).

Needle biopsy of the liver was performed after determination of normal bleeding, clotting, and clot-retraction times. An intercostal approach was used in all cases, and the Roth-Turkel needle was employed. Tissue obtained was immediately fixed in 10% formalin; sections were stained with hematoxylin and eosin, and in some cases with the Van Gieson stain in addition.

TABLE 1.—*Characterization of Cases of Obesity*

Case No.	Age, Yr.	Duration of Obesity, Yr.	Height, In.	Weight, Lb.	% Over-Weight	Large Liver	Large Spleen
1	41	8	63	230	81	+	+
2	34	8	63	250	97	..	..
3	54	6	68	242	67	+	+
4	51	35	69	235	58	..	..
5	59	25	73	250	50	+	..
6	56	10	69	254	70	+	+
7	36	32	70	259	69	..	..
8	28	8	67	212	50	..	..
9	53	39	71	235	50	..	..
10	44	30	67	237	68	..	..
11	71	60	65	206	54	..	..
12	45	30	71	299	91	..	..
13	50	40	70	257	68	+	+
14	54	50	70	252	64	..	+
15	23	18	67	213	51	..	..
16	53	40	65	214	60	+	..
17	56	14	64	206	58	..	..
18	27	8	69	258	73	..	..
19	60	45	64	209	61	..	..
20	57	45	70	245	62	..	..

RESULTS

Characterization of Cases (Table 1).—The patients ranged from 23 to 71 years of age, averaging 48.1 years. Their heights ranged from 63 to 73 in. (160 to 185 cm.), averaging 67.8 in. (172 cm.). Their weights ranged from 206 to 299 lb. (93 to 136 kg.), averaging 238.2 lb. (108 kg.). Their percentages of overweight above ideal standards ranged from 50 (below which figure patients were excluded from this study) to 97, and averaged 65%.

Liver, Spleen and Gall-Bladder Visualizations (Table 1).—All 20 patients showed normal dye concentration and emptying of the gall bladder with the Graham-Cole test, this being a criterion of selection of the subjects. Liver and spleen visualizations showed slight enlargement of both organs in two men, of the liver alone in two, and of the spleen alone in three; all enlargements were characterized as slight in degree.

Dextrose-Tolerance Test (Table 2).—Five-hour oral dextrose-tolerance tests were performed on 19 subjects, values being determined on venous blood. Peak

concentrations exceeded 180 mg. per 100 cc. in nine instances, ranging from 182 to 300 mg., although only one of these showed an abnormal fasting level (146 mg.). Return to normal levels occurred within two hours in one and within three hours in five of these men, within four hours in two subjects, and within six hours in one. Of the 11 men with normal peak concentrations, 3 required three hours to return to normal levels. One patient (Case 11) reached an asymptomatic hypoglycemic level (43 mg.) at the fourth hour.

Thus, impaired dextrose tolerance was demonstrated in approximately half the patients with obesity, a proportion which corresponds closely to that in previously reported studies of larger groups. The impairment of tolerance in each patient was attributed to the obesity, and glycosuria was absent while the high-protein, low-calory diet was taken. In no case was insulin needed or used. One patient (Case 6), with a fasting hyperglycemia, steadily mounting glucose level to the second hour, and return to normal only after five hours, may certainly be characterized as diabetic. But this patient was included in the series because sugar was entirely absent from a 24-hour collection of urine and normal fasting blood sugar levels were obtained when the patient was taking the high-protein, low-calory diet.

TABLE 2.—*Dextrose Tolerance in Obesity**

Case No.	0 Hr.	½ Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.
1	102	164	**265**	**165**	111	62	73
2	108	135	131	**128**	86	94	89
3	78	114	126	102	108	81	83
4	120	**238**	**300**	**259**	102	..	..
5	92	137	141	**124**	74	68	70
6	**146**	177	**223**	**264**	**201**	**162**	**125**
7	...	...	...	...	...	..	..
8	97	160	159	118	92	77	87
9	113	128	**194**	**155**	89	90	99
10	106	147	**196**	117	56	84	83
11	95	118	174	**133**	62	**43**	63
12	103	122	107	98	118	84	91
13	78	128	137	102	64	76	66
14	110	177	**241**	**191**	116	88	92
15	76	122	118	119	105	50	**74**
16	104	148	**194**	**190**	**138**	82	78
17	96	150	**186**	**166**	100	73	70
18	84	133	139	118	78	88	89
19	106	**182**	157	104	67	70	84
20	104	176	180	116	103	88	98

* Numbers in boldface type are abnormal values.

Liver-Function Studies (Table 3).—The sulfobromophthalein retention was abnormal in all 20 patients, ranging from 6 to 33% retention at 45 minutes, with an average of 14.7%. Ten subjects (50%) showed abnormal thymol turbidity of the serum, ranging from 5 to 10 units. Ten patients (50%) had abnormally high serum cholesterol values, ranging from 267 to 416 mg. per 100 cc.; seven of these were included among those with abnormal thymol turbidity. Six patients of 19 (32%) showed abnormally high urobilinogen output in at least one of three two-hour urine specimens, ranging from 1.12 to 1.85 Ehrlich units. Five patients of 19 (26%) had abnormally high serum alkaline phosphatase levels, rang-

ing from 5.7 to 11.5 Bodansky units. Four men (20%) had a serum cephalin-cholesterol flocculation of 2 or 3 + in 48 hours; of these, three had impaired dextrose-tolerance curves, and the fourth was the one person for whom dextrose tolerance was not determined. Four subjects (20%) showed low cholesterol ester ratios, ranging from 53 to 58% of their total cholesterol values. The prothrombin time was considered abnormally prolonged in three patients (15%). The one-minute direct and total serum bilirubin values were abnormal in one patient each (not the same person), while the serum albumin and globulin were normal in all 20 subjects.

TABLE 3.—*Liver-Function Studies in Obesity**

Case No.	B. S. P. Retention, %	Bilirubin, Mg.		Phosphatase, Bodansky Units	Cephalin Flocculation	Thymol Turbidity, Units	Albumin, Gm.	Globulin, Gm.	Cholesterol		Prothrombin Time, Sec.	Urine Urobilinogen, Ehrlich Units/2 Hr.	Total Abnormal Tests
		Total	1-Min.						Total, Mg.	Ester, %			
1	**29**	0.9	0	5.3	0	**5.5**	5.3	2.3	**374**	**53**	**13.2**	0.64	5
2	**12**	0.8	0	**7.7**	0	3.0	5.4	2.0	244	65	12.8	**1.84**	3
3	**18**	0.6	0	4.1	0	**5.5**	5.1	1.9	154	62	10.6	**1.12**	3
4	**8**	0.6	0	5.0	**2+**	2.5	4.6	2.3	238	**58**	11.4	0.77	3
5	**18**	0.6	0	5.0	0	**5.0**	4.8	2.1	**294**	**56**	**14.5**	0.64	5
6	**10**	0.6	0	3.6	**1+**	2.6	4.1	2.1	172	61	11.0	0.64	1
7	**6**	0.4	0	...	**3+**	**10.0**	4.8	2.4	222	62	12.6	**1.14**	4
8	**22**	1.0	0	3.2	**1+**	**5.0**	4.9	2.5	**267**	62	**14.8**	**1.9**	5
9	**13**	0.5	0	5.0	**2+**	4.0	4.8	2.3	224	62	11.8	0.51	2
10	**9**	**1.2**	0.1	**5.7**	**2+**	**5.5**	4.9	2.2	234	62	11.0	0.99	5
11	**19**	0.6	0	4.3	0	1.5	5.2	2.3	**318**	60	12.3	0.55	2
12	**7**	0.6	0	**11.5**	**1+**	4.0	4.4	2.6	**276**	67	11.4	0.33	3
13	**26**	0.7	**0.3**	**7.5**	**1+**	**5.4**	4.8	2.5	**333**	**57**	12.8	**1.85**	7
14	**6**	1.0	0	4.8	0	**7.4**	5.5	2.0	**285**	62	12.6	0.98	3
15	**11**	0.6	0	5.0	0	**3.0**	5.4	1.8	250	63	12.5	**1.22**	2
16	**33**	0.6	0	**7.6**	0	4.0	5.1	2.5	185	60	12.6	0.72	2
17	**15**	0.6	0	2.7	0	**6.5**	4.8	2.3	**276**	61	11.2	0.69	3
18	**9**	0.6	0	4.7	0	3.1	4.8	2.3	**283**	61	11.6	0.80	2
19	**17**	0.6	0	2.0	0	**6.7**	5.0	2.2	**416**	**57**	10.8	....	4
20	**6**	0.5	0	2.9	0	2.8	4.9	1.7	148	63	12.5	0.54	1
Total Abnormal	20	1	1	5	4	10	0	0	10	5	3	6	3.25 (Average per Case)
% Abnormal	100	5	5	26	20	50	0	0	50	25	15	32	

* Numbers in boldface type are abnormal values.

Of the 20 patients, 1 showed seven abnormal liver-function tests, 4 showed five and 2 showed four abnormal tests, 6 showed three and 5 showed two abnormal tests, and 2 showed only the abnormal sulfobromophthalein retention. The average number of abnormal liver-function tests was 3.25.

Needle Biopsy of the Liver (Table 4).—This was performed in 19 cases. Because of the subjective nature of the grading and the vagueness of knowledge of the limits of normality in the histology of the biopsied liver, changes recorded as slight are excluded from the totals. Degenerative parenchymal-cell changes (fading, pyknosis, chromatolysis and ballooning of nuclei, loss of granularity, smudging or intense eosinophilic staining of cytoplasm, and loss of cell contours) occurred in moderate or marked degree in 11 patients, or 58%. Changes interpreted as parenchymal-cell regeneration (multiple nucleoli, numerous double and occasional triple nuclei,

marked variation in size and staining of nuclei and in size of cells) were present in moderate degree in 10 subjects, or 53%. The same number of men (53%) showed fatty change of moderate or marked degree. Bile-pigment retention in parenchymal cells was of moderate degree in nine patients (47%). Moderate or marked increase

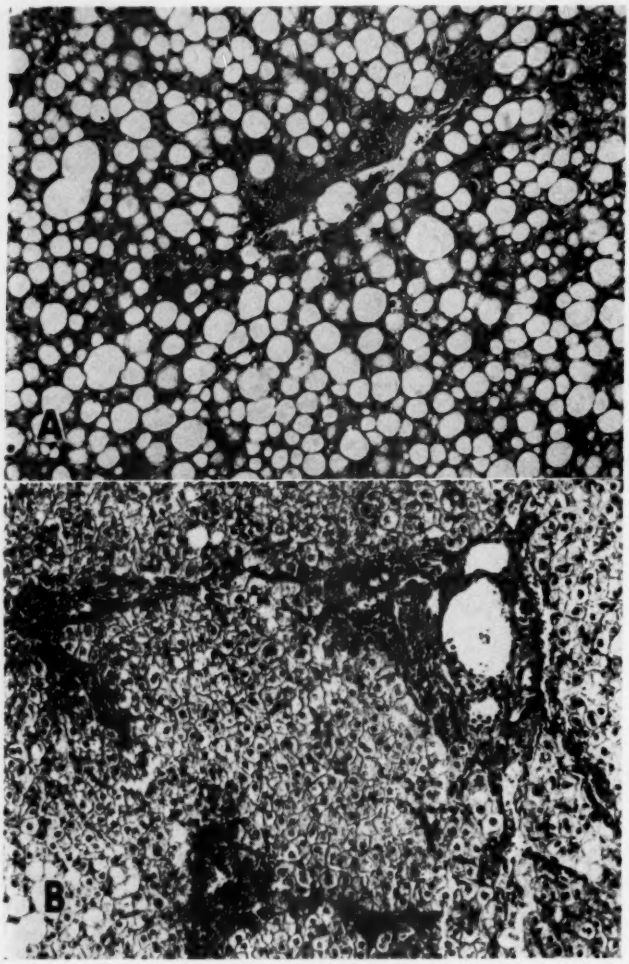

Fig. 1.—Photomicrographs; × 140. *A* (Case 3), cytoplasmic fat vacuolation; hematoxylin and eosin stain. *B* (Case 14), early cirrhotic radiation of fibrous strands; Van Gieson stain.

in periportal fibrous tissue was present in the same number (47%). None of these showed actual cirrhosis, since such persons were excluded from the series, but in one patient (Case 14) there was some tendency for the fibrous tissue to interconnect (Fig. 1*B*), which probably represents an early transition toward eventual cirrhosis.

Six patients (32%) showed moderate or marked degrees of periportal cellular infiltration, and two (11%) showed moderate prominence of Kupffer cells. One patient (5%) was recorded as showing a moderate degree of focal necrosis.

Of the eight categories used as criteria, changes of moderate or marked degree in six were encountered in one subject, in five in two subjects, in four in five, in three in five, in two in two, in one in three, and in none in one subject. The last patient showed a slight degree of change in seven of the eight categories. Thus, no biopsy specimen was recorded as normal, and all but one (95%) were abnormal to at least moderate degree by at least one criterion.

TABLE 4.—*Histologic Changes in Liver in Obesity**

Case No.	Liver Cell Degeneration	Focal Necrosis	Bile Pigment Retention	Fat Vacuolation	Liver Cell Regeneration	Kupffer Cell Mobilization	Periportal Cellular Infiltrate	Periportal Fibrosis	Total Abnormal†
1	2	0	0	2	1	1	2	2	4
2	1	1	2	1	1	0	1	1	1
3	2	1	0	3	2	0	1	1	3
4	1	0	2	0	1	0	1	1	1
5	2	1	2	1	2	1	1	2	4
6	3	1	2	2	2	1	1	1	4
7	2	1	1	2	2	1	3	2	5
8	1	0	1	1	2	1	1	2	2
9	1	0	1	0	2	1	1	0	1
10	2	1	1	3	2	1	1	1	3
11	2	1	0	1	2	2	3	2	5
12	2	1	1	2	2	1	1	1	3
13	2	1	2	1	1	1	2	2	4
14	2	2	1	2	1	2	2	3	6
15	1	0	1	1	1	1	1	1	0
16	..	..	..	..	..	..	..	..	..
17	1	1	2	1	1	1	1	3	2
18	1	1	2	2	1	1	2	1	3
19	1	1	2	2	2	1	1	2	4
20	2	1	2	2	1	1	1	1	3
Total Abnormal †	11	1	9	10	10	2	6	9	3.1 (Average per Case)
% Abnormal	58	5	47	53	53	11	32	47	

* 1 is slight; 2, moderate, and 3, marked.
† Only moderate and marked changes are totaled.

CORRELATIONS

Degree of Obesity.—Within the limits of this study, there were no significant correlations between the degree of obesity and the results of any of the studies recorded.

Duration of Obesity.—This averaged 27.6 years, ranging from 8 to 60 years, but the figures obtained represented approximations at best. For nine subjects obesity was recorded as being of less than 30 years' duration, averaging 11.7 years, and for 11 subjects, as being present 30 years or more, averaging 40.6 years. Evaluation of the studies in these two groups separately reveals no difference of statistical significance in the sulfobromophthalein retention figures or in the dextrose tolerance. The four positive cephalin flocculations occurred in persons with obesity of long duration, as did the two bilirubin elevations and four of the five elevated

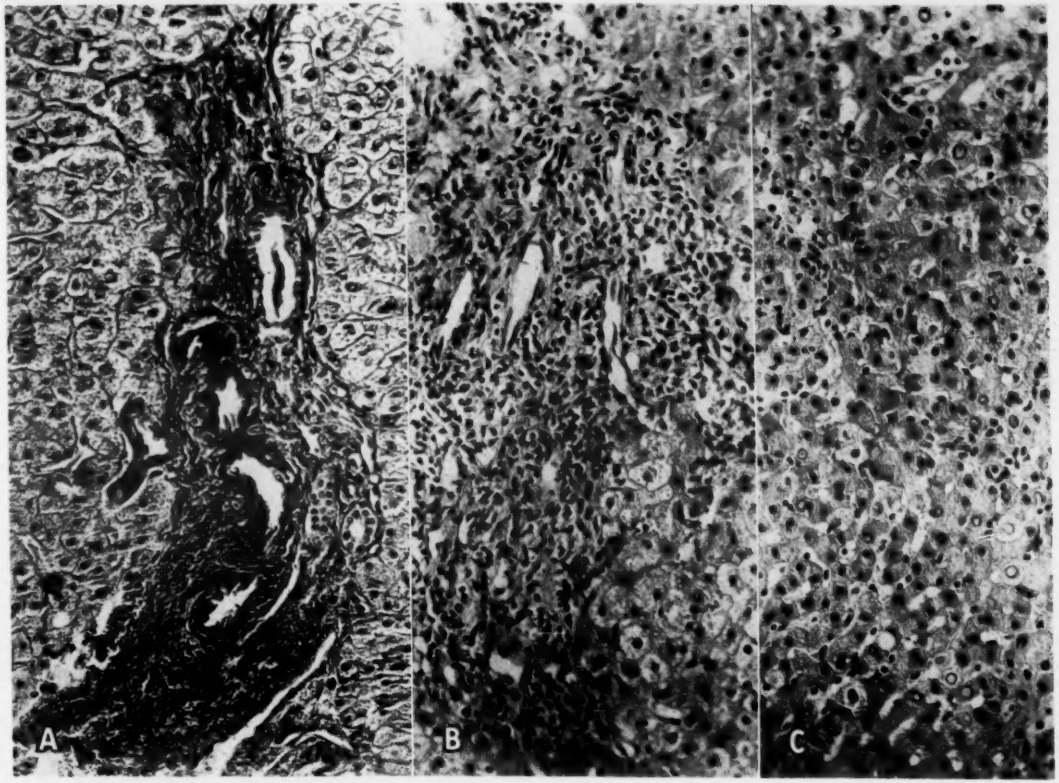

Fig. 2.—Photomicrographs; × 215. *A* (Case 19), periportal fibrosis; Van Gieson stain. *B* (Case 7), periportal cellular infiltration; hematoxylin and eosin stain. *C* (Case 6), degenerative parenchymal-cell changes; hematoxylin and eosin stain. Note also Figure 4*C*.

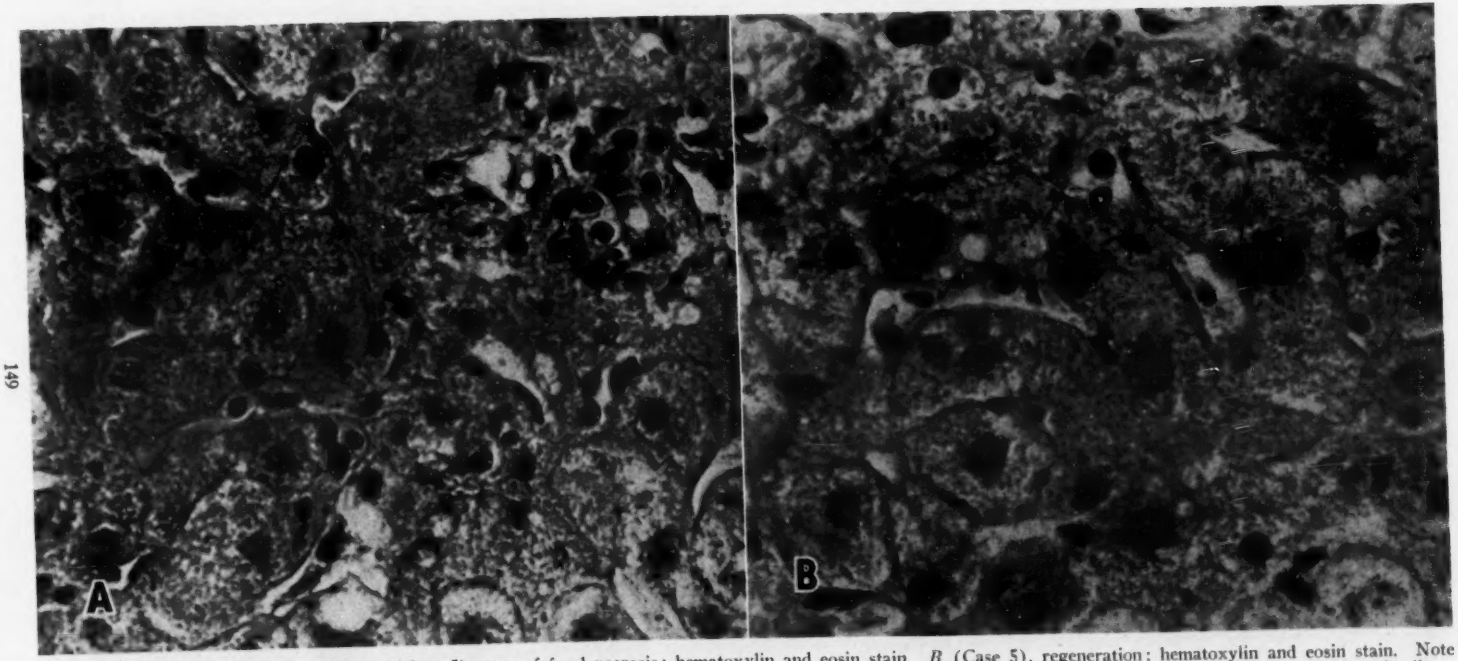

Fig. 3.—Photomicrographs; × 690. *A* (Case 5), area of focal necrosis; hematoxylin and eosin stain. *B* (Case 5), regeneration; hematoxylin and eosin stain. Note size of regenerating cells, which at this magnification resemble photomicrographs of higher power. Multiple nucleoli, double-nucleated cells, and one triple-nucleated cell are seen.

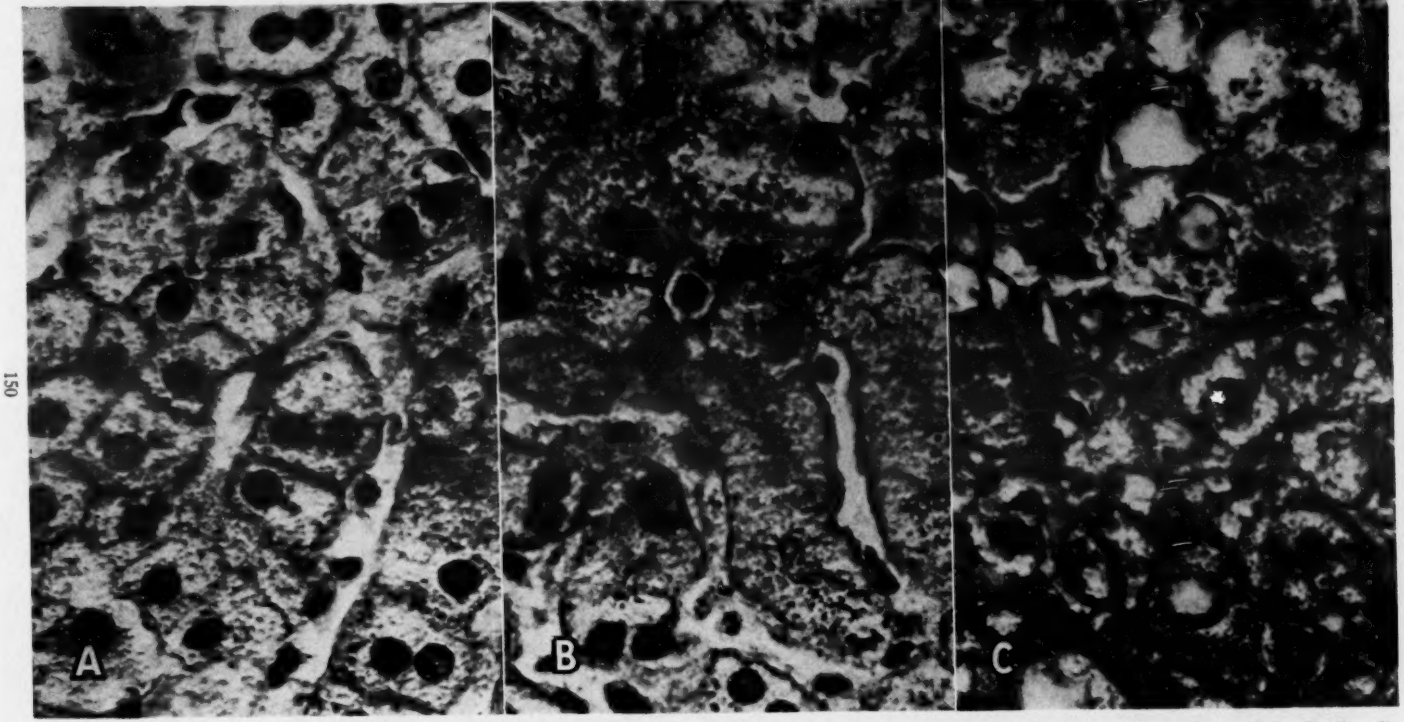

Fig. 4.—Photomicrographs; × 925. *A* (Case 14), Kupffer-cell mobilization; Van Gieson stain. A rare mitotic figure is seen in a liver cell at top left. *B* (Case 5), cytoplasmic bile-pigment retention; hematoxylin and eosin. *C* (Case 14), degenerative parenchymal cell changes; hematoxylin and eosin. Note also Figure 2*C*.

alkaline phosphatase determinations. On the other hand, the three elevated prothrombin times and four of the six high urinary urobilinogen outputs occurred in the patients whose obesity was of shorter duration.

The liver biopsy specimens revealed a significant difference between the two groups (Table 5). In all categories except bile-pigment retention and fat vacuolation, the patients having obesity of longer duration showed a higher incidence of abnormality than did those with obesity of shorter duration. Liver-cell damage (degeneration and necrosis) was recorded as of moderate or severe degree twice as often (eight instances compared with four). Regeneration was pronounced in six patients compared with four having obesity of shorter duration. Cellular reaction (periportal infiltrate and Kupffer-cell prominence) occurred in moderate or marked degree six times in patients with long duration and only twice in those with short duration. The difference in incidence of periportal fibrosis is not significant.

Liver and Spleen Enlargements.—The seven men who showed slight enlargement of one or both of these organs by roentgen visualization averaged a sulfobromo-

TABLE 5.—*Histologic Changes of Liver in Relation to Duration of Obesity**

	< 30-Yr. Duration (9 Cases)	30+-Yr. Duration (10 Cases)
Liver-cell degeneration	4	7
Focal necrosis	0	1
Bile-pigment retention	5	4
Fat vacuolation	5	5
Liver-cell regeneration	4	6
Kupffer-cell mobilization	0	2
Periportal cellular infiltration	2	4
Periportal fibrosis	4	5
Total abnormalities per case	2.7	3.4
Average duration of obesity, yr.	11.7	40.6
Average age, yr.	35.3	52.1

* Only moderate or severe changes are tabulated.

phthalein retention of 20.0%, compared with 14.7% for the entire series. Other liver-function tests showed no significant correlations with these organ enlargements, nor did the carbohydrate tolerance or the histologic characteristics of the liver.

Dextrose-Tolerance Test.—The average age of the nine obese patients with impaired carbohydrate tolerance was 52.0 years, compared with 40.6 years for the seven with the nondiabetic curves. The duration of obesity as obtained by history, often approximate, averaged 30.1 years for the diabetic and 22.1 for the nondiabetic patients. The diabetic group averaged 63.3% overweight, the nondiabetic, 66.0%. The cephalin-cholesterol flocculation test was positive for three of the diabetic group and for none of the nondiabetic subjects. On the other hand, urinary urobilinogen was elevated in none of the diabetic group and in four of the nondiabetic men. Other liver-function studies lacked significant correlation with the dextrose tolerance. The histologic abnormalities also failed to correlate significantly with carbohydrate tolerance.

Liver-Function Tests and Liver Histology.—Abnormalities determined by these two methods of study failed to show significant correlations when compared.

COMMENT

The food requirement of the obese person, even at static weight, is greatly increased over the normal for his height. His basal metabolism may be increased more than one-third because of the increased surface area, even though the basal metabolism per square meter of surface area is unchanged.[13] His total metabolism is similarly increased, not only proportionately to the larger surface area but additionally because of the increased work required to move the greater body mass.[14] Finally, the specific dynamic action of the ingested foodstuff is increased proportionately to its quantity.[15] The total food requirement of an obese person may reach twice his requirement at ideal weight.

The metabolic turnover of the food ingested is largely a function of the liver, to which the assimilated foodstuffs are first delivered. The total specific dynamic heat evolved is an effect of such intermediary metabolism and may be taken as a measure of the work required to make that food available. The liver is responsible for most of this work.[16] It may be anticipated, therefore, that the chronic strain of an overload upon the liver due to the excessive food ingestion necessitated by the obese state will eventually result in liver damage, just as the chronic strain of arterial hypertension eventually results in left ventricular failure of the heart. The finding in this series of cases that the extent of anatomical liver damage was correlated with the duration rather than with the degree of obesity is compatible with such a supposition. The liver damage which occurs in thyrotoxicosis[17] and in diabetes mellitus[18] may be similarly related to the increased metabolic load imposed upon the liver in these diseases.

Inasmuch as the liver has a remarkable capacity for regeneration,[19] some doubt may reasonably be entertained regarding the possibility of a chronic overload of work producing liver injury. Additional limiting factors which may play a role in the liver disturbance of obesity should be sought. One of these may well be the customary diet of the obese, which is characteristically rich in carbohydrates and fats and poor in proteins.[20] The total protein intake may not be low, as ordinarily

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20. Dunlop, D. M., and Murray Lyon, R. M.: A Study of 523 Cases of Obesity, Edinburgh M. J. **38**:561-577, 1931. Bruch, H.: Obesity in Childhood: Physiologic and Psychologic Aspects of Food Intake of Obese Children, Am. J. Dis. Child. **59**:739-781, 1940. Rony, H. R: Obesity and Leanness, Philadelphia, Lea & Febiger, 1940.

evaluated, but its proportion is low in relation to the total caloric intake. Precisely this disproportion has been shown to be responsible for liver damage in rats.[21] When maintained on a marginal protein intake, these animals showed fatty and fibrotic changes in the liver following increase in the total caloric intake by added sugar or alcohol, these two sources of calories producing indistinguishable results. Addition of protein or choline to the diet prevented the appearance of liver damage. Thus, it appears likely that the high-carbohydrate, proportionately low-protein intake of the obese patient may have the same hepatic effects clinicians have learned to expect in the chronic alcoholic.

Of interest in relation to the preference of obese persons for fatty as well as carbohydrate foods is the observation that hereditarily obese mice allowed a free choice of diet ate considerably more fat and less protein than nonobese members of the same strain.[22] A high-fat diet with proportionately low protein has long been used as a standard method of producing liver damage in animals.[23]

Vitamin B deficiencies played no role in the above-mentioned animal studies, since generous supplements were included in the basal diets. Actually, liver damage has been produced by the appetite stimulation and weight gain effected by the administration of large doses of the vitamins of the B complex, with fatty liver resulting in direct proportion to the increased food intake.[24] This occurs with either high-fat or high-carbohydrate diets and is prevented by ingestion of choline or protein in amounts which vary directly with the amount of food eaten.[25]

The patients with obesity in this series were carefully questioned regarding their dietary habits, and, with a single exception, they recounted their fondness for foods rich in carbohydrate and fat and poor in protein. The one exception (Case 18) related a fantastic story of fondness for the ingestion of huge beefsteaks, which is difficult to evaluate, inasmuch as he was a psychiatric patient whose psychiatrist stated was given to pathologic lying, and since he had, unfortunately, already been made familiar with the high-protein regimen used at the hospital in obesity and liver disease. Another subject (Case 1), an aide at this hospital, ingested the contents of 20 or more bottles of coca-cola® per day, these being available at dispensing stations in various parts of the hospital. This was a total of 1,600 calories of sugar, in addition to the usual meals served to the hospital employees, among whom this patient was also distinguished for his appetite.[1] This patient's sugar supplement is isocaloric with 1 pt. (473 cc.) or more of whisky. It was interest in this case, in view of the Toronto report [21] referred to above, which stimulated this study of the liver in obesity.

21. Best, C. H.; Hartroft, W. S.; Lucas, C. C., and Ridout, J. H.: Liver Damage Produced by Feeding Alcohol or Sugar and Its Prevention by Choline, Brit. M. J. **2**:1001-1006, 1949.

22. Mayer, J.; Dickie, M. M.; Bates, M. W., and Vitale, J. J.: Free Selection of Nutrients by Hereditarily Obese Mice, Science **113**:745-746, 1951.

23. Chaikoff, I. L., and Connor, C. L.: Production of Cirrhosis of the Liver of the Normal Dog by High Fat Diets, Proc. Soc. Exper. Biol. & Med. **43**:638-641, 1940.

24. McHenry, E. W., and Gavin, G.: The B Vitamins and Fat Metabolism: I. Effects of Thiamine, Riboflavin, and Rice-Polish Concentrate upon Body Fat, J. Biol. Chem. **125**:653-660, 1938.

25. Engel, R. W.: The Relation of B-Vitamins and Dietary Fat to the Lipotropic Action of Choline, J. Nutrition **24**:175-185, 1942.

The higher food intake of the obese, with its attendant increase in total metabolism, requires a higher intake of the vitamins of the B complex.[26] The fatty and processed carbohydrate foods preferred by the obese are generally poor in these vitamins. Despite ingestion of what may be a normal vitamin requirement for the average dietary, the obese patient may be suffering a chronic deficiency of these vitamins relative to his greatly increased metabolic requirements. Such a deficiency may further contribute to the causation of the liver damage in these patients.[27] The parallelism between the obese and the alcoholic is here again evident.

Even though the liver damage of the chronic alcoholic may be presumed to occur in a manner similar to that of the obese, chronic alcoholics were excluded from this series of cases, since the project was designed to discover liver damage, if present, in the obese in the absence of any other responsible factors. So cautious was the selection that 18 months was required to accumulate 20 subjects. Excluded also were obese patients with hepatic cirrhosis, although in the light of the results of the study, the changes in such persons, lacking other causes, may well represent the end-result of the liver damage in the obese. Mention is made of these exclusions in order to indicate that the results of this study are likely to represent the minimal degree of liver damage to be found in the obese, and that the average obese person —including those with diabetes, alcoholism, cirrhosis, history of jaundice, or gallbladder disease—is hepatically a sicker patient than those considered in this study.

If cirrhosis of the liver is an end-result of the hepatic damage of the obese, it should be reflected in insurance mortality data. A recent survey of mortalities among overweight persons accepted for substandard insurance [28] reveals that overweight men died of cirrhosis of the liver in a ratio of actual to expected deaths of 249%. Among the other causes of death, the ratio was higher than this only for diabetes mellitus. In contrast to alcoholism, obesity in association with hepatic cirrhosis has not been noted as a frequent clinical phenomenon. This may be due, at least in part, to the frequency of anorexia and weight loss in established cirrhosis, whereas the appetite for alcohol continues unimpaired.

Among insured overweight women, the ratio of actual to expected deaths from cirrhosis of the liver was 147%, although the excess mortality from all causes showed no sex difference. This suggests that obesity is better tolerated by the female than by the male liver. A further indication of such a sex difference in tolerance of the liver to obesity is the greater incidence of impaired carbohydrate tolerance in obese males than in obese females.[5] The nature of the hospital population available to me limited this study to the male. A similar study carried out on obese females would be of interest.

The demonstration of the existence of hepatic damage in obesity poses the problem of protection of the liver during the dietary reduction program. The reducing diet is metabolically a high-fat diet, since body fat supplies the caloric deficit of the diet. The protein or choline requirement is correspondingly high,[25] as is the

26. Robinson, F. A.: The Vitamin B Complex, New York, John Wiley & Sons, Inc., 1951.

27. Patek, A. J., Jr.: Evaluation of Dietary Factors in Treatment of Laennec's Cirrhosis of the Liver, J. Mt. Sinai Hosp. **14**:1-7, 1947.

28. Dublin, L. I., and Marks, H. H.: Mortality Among Insured Overweights in Recent Years, Tr. A. Life Insur. M. Dir. America **35**:235-266, 1952; cited by Dublin, L. I.: Personal communication to the author.

requirement for vitamins of the B complex.[27] The food ingested should contain, therefore, as much protein as possible, and supplementary choline and B vitamins should be administered. The patients in this series have been given a 1,200- to 1,500-calory diet containing 120 to 150 gm. of protein; 6 gm. of choline and twice the minimum standard daily requirements of the B vitamins are prescribed in addition. Beef liver, most of the fish foods, and milk protein (skim milk, cottage cheese) are important components of this low-calory, high-protein diet; none of the meats supplies as high a ratio of protein to fat as do these foods. Commercial protein supplements usually contain a high-carbohydrate content which is undesirable for the low-calory diet.

These patients were not hospitalized for prolonged dietary therapy, except for certain psychiatric patients who did not reliably follow their diets. Follow-up study on some, but not all, of the others, indicates that none has thus far attained normal weight. Investigation of the reversibility of the liver damage of obesity in this group of patients is, therefore, not yet feasible. Two patients restudied (Cases 1 and 14) after partial weight loss had improved liver-function tests, and the liver biopsy specimens showed less fat vacuolation. One of the two biopsy specimens was considered to show beginning pseudolobulation by fibrous tissue, not previously present (Case 1).

In common with the observations of others, I have found as much difficulty and discouragement in dealing with the craving for carbohydrate- and fat-rich foods manifested by the obese as with the craving for alcohol of the chronic alcoholic. Psychologic determinants are undoubtedly important in these patients, but the demonstration of hypothalamic feeding and inhibiting centers,[29] as well as the production of hereditary obesity in mice,[30] should caution against lightly assigning the problem of the causation of obesity entirely to the psychologic sphere.

SUMMARY

Summary of Observations.—After careful screening to exclude all past or present illness which might affect the liver, 20 obese men who were between 50 and 100% overweight were studied for liver disturbance by laboratory tests and needle biopsy.

All subjects showed both laboratory and histologic evidence of liver disease.

Approximately half the subjects showed impairment of dextrose tolerance, in no case requiring insulin. The carbohydrate tolerance failed to correlate with other evidences of liver disease.

The sulfobromophthalein (bromsulphalein®) retention was abnormal in all the subjects. Thymol turbidity and serum cholesterol were abnormal in half of them. One-third showed abnormally high urobilinogen outputs in the urine. One-fourth had high serum alkaline phosphatase levels. Cephalin-cholesterol flocculation and cholesterol ester ratios were abnormal in one-fifth of the group. Serum albumin and globulin were normal in all subjects.

On needle biopsy of the liver, degenerative changes of the parenchymal cells, fatty change, bile-pigment retention, parenchymal-cell regeneration, and periportal

29. Anand, B. K., and Brobeck, J. R.: Localization of a "Feeding Center" in the Hypothalamus of the Rat, Proc. Soc. Exper. Biol. & Med. **77**:323-324, 1951.

30. Danforth, C. H.: Hereditary Adiposity in Mice, J. Hered. **18**:153-162, 1927.

fibrosis were present to at least moderate degree in approximately half the subjects. One-third of them showed cellular infiltration of the periportal spaces more than slight in degree. In none was the liver entirely normal.

The duration of obesity, but not its degree, proved significantly related to the extent of anatomical disturbance of the liver. The liver-function tests did not show comparable correlation.

Summary of Argument.—Experimental obesity in animals is uniformly accompanied with hepatic damage. Previous evidence of hepatic damage in human obesity is limited to disturbances of carbohydrate tolerance. The present study indicates the uniform presence of liver damage in human obesity, as manifested by liver-function tests and biopsies. Confirmation is found in the greatly increased incidence of cirrhosis of the liver in the obese, as indicated by insurance statistics. An explanation of the liver damage of obesity is found in (*a*) the high caloric requirement of the obese, constituting a functional overload upon the liver, (*b*) the high-carbohydrate, high-fat, low-protein diet customary among the obese, and (*c*) the increased requirement of choline and vitamins of the B complex imposed by the quantitative and qualitative nature of the obese diet. The reducing program should consist of a high-protein diet supplemented by choline and vitamins of the B complex.

PRIMARY PULMONARY ARTERIOLOSCLEROSIS

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THE PURPOSE of this paper is to describe the disease known as primary pulmonary arteriolosclerosis, to review the important literature, and to report three additional cases.

Primary pulmonary arteriolosclerosis may be defined as a rare, progressive, fatal disease of unknown causation characterized by an extensive narrowing of the pulmonary arterioles by an arteriosclerotic process. The disease is uniformly associated with right ventricular enlargement. Recognition is difficult because, by definition, all pathologic processes now known to cause pulmonary arteriolosclerosis must be eliminated by detailed clinical and pathologic examination.

Interest in the problem of pulmonary arteriosclerosis was evident as early as 1706 in the writings of Vieussens.[1] However, it was not until the early 19th century that the subject attracted sufficient attention to appear again in the literature in the writings of Kreysig [2] and Andral.[3] This entity actually was not appreciated until the latter part of that century, when the cases of Klob,[4] Wolfram,[5] and Romberg [6] were described. Since microscopic examination is necessary before diagnosis can be confirmed, it fell to Mönckeberg [7] in 1907 to achieve the first authenticated description

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1. Vieussens, cited by Giroux, L.: Sclérose et athérome de l'artère pulmonaire: Role des conditions mécaniques, Arch. mal. coeur **3**:218, 1910.

2. Kreysig, F. L.: Les maladies du coeur, Vol. 3, cited by Giroux, L.: Sclérose et athérome de l'artère pulmonaire: Role des conditions mécaniques, Arch. mal. coeur **3**:218, 1910.

3. Andral, A.: A Treatise on Pathological Anatomy, translated by R. Townsend and W. West, London, Longman and Co., G. and T. Underwood, 1831, Vol. 2, p. 396.

4. Klob: Wien. Wchnbl. **21**:45, 1865, cited by Romberg, E.: Über Sklerose der Lungenarterie, Deutsches Arch. klin. Med. **48**:197, 1891.

5. Wolfram, A.: Gaz. lek., Nos. 24 and 25, 1883; cited by Giroux, L.: Sclérose et athérome de l'artère pulmonaire: Role des conditions mécaniques, Arch. mal. coeur **3**:218, 1910.

6. Romberg, E.: Über Sklerose der Lungenarterie, Deutsche Arch. klin. Med. **48**:197, 1891.

7. Mönckeberg, J. G.: Über die genuine Arteriosklerose der Lungenarterie, Deutsche med. Wchnschr. **33**:1243, 1907.

of primary pulmonary arteriolosclerosis. Attention was drawn to the clinical and pathologic picture of pulmonary arteriosclerosis by observers in many countries, including Posselt [8] and Ljungdahl [9] in Germany, Laubry [10] and Giroux [11] in France, Gamma [12] in Italy, and Rogers [13] in England. The man whose name is most closely associated with pulmonary arteriosclerosis, Abel Ayerza, strangely enough neither contributed to the literature on this subject nor believed that the clinical picture in patients he described as *"cardíacos negros"* (black cardiacs) was due to vascular involvement.[14] The first published use of the term Ayerza's disease was in a doctoral thesis by Marty,[15] in which he cited a clinical demonstration given by Prof. Abel Ayerza on Aug. 20, 1901. Two students of Ayerza, Escudero [16] and Arrillaga,[17] later popularized this syndrome and focused attention on the vascular pathology involved. Barlaro [18] in 1917 attributed the vascular lesions to syphilis, and strong support for this belief has persisted in the Spanish literature. Warthin [19] in this country also championed this viewpoint. Although more than 100 cases of so-called primary pulmonary arteriosclerosis have been described in the literature with variable clinical and pathologic characteristics, only one-third have survived the critical reviews of

8. Posselt, A.: Die klinische Diagnose der Pulmonalarteriensklerose, München. med. Wchnschr. **55**:1625, 1908; Die Erkrankungen der Lungenschlagader, Ergebn. allg. Path. u. path. Anat. **13**:298, 1909; Zur Pathologie und Klinik der primären Atherosklerosis pulmonalis, Wien. Arch. inn. Med. **11**:357, 1925.

9. Ljungdahl, M.: Untersuchungen über die Arteriosklerose des kleinen Kreislaufs, Wiesbaden, J. F. Bergmann, 1915.

10. Laubry, C., and Parvu, M.: Artério-sclérose généralisée de l'artère pulmonaire, Bull. et mém. Soc. méd. hôp. Paris **27**:1320, 1909. Laubry, C., and Thomas, M.: Les lésions de l'artère pulmonaire et leurs conséquences au cours du rétrécissement mitral, ibid. **50**:639, 1926.

11. Giroux, L.: Sclérose et athérome de l'artère pulmonaire: Role des conditions mécaniques, Arch. mal. coeur **3**:218, 1910; Sclérose et athérome de l'artére pulmonaire, Thése de Paris, No. 149, 1910.

12. Gamma, C.: Sull' arteriosclerosi polmonare, Pathologica **13**:207, 1921.

13. Rogers, L.: Extensive Atheroma and Dilatation of the Pulmonary Arteries, Without Marked Valvular Lesions, as a Not Very Rare Cause of Fatal Cardiac Disease in Bengal, Quart. J. Med. **2**:1, 1908.

14. Ayerza, L.: Semana méd. **23**:386, 1925; cited by Montgomery, G. L.: A Case of Pulmonary Artery Thrombosis with Ayerza's Syndrome, J. Path. & Bact. **41**:221, 1935.

15. Marty, C. A.: La tension arterial en la tuberculosis pulmonaire, Buenos Aires, 1909, p. 45; cited by Warthin, A. S.: A Case of Ayerza's Disease: Chronic Cyanosis, Dyspnea and Erythremia, Associated with Syphilitic Arteriosclerosis of the Pulmonary Arteries, Tr. A. Am. Physicians **34**:218, 1919.

16. Escudero, P.: Les cardiaques noirs et la maladie de Ayerza, Arch. mal. coeur **19**:439, 1926.

17. Arrillaga, F. C.: Sclérose de l'artère pulmonaire secondaire à certains états pulmonaires chroniques, Arch. mal. coeur **6**:518, 1913; Sclérose de l'artére pulmonaire, Bull. et mém. Soc. méd. hôp. Paris **48**:292, 1924

18. Barlaro: Rev. Asoc. méd. argent. **26**:121, 1917; cited by Brachetto-Brian, D.: Concepto anatomo-pathologico de los cardiacos negros de Ayerza, Rev. Soc. med. int. y tisiol. **6**:821, 1925.

19. Warthin, A. S.: Syphilis of the Pulmonary Artery: Syphilitic Aneurysm of the Left Upper Division; Demonstration of the Spirochete Pallida in Wall of Artery and Aneurysmal Sac, Am. J. Syph. **1**:693, 1917; A Case of Ayerza's Disease: Chronic Cyanosis, Dyspnea and Erythremia, Associated with Syphilitic Arteriosclerosis of the Pulmonary Arteries, Tr. A. Am. Physicians **34**:218, 1919.

other writers.[20] Moschcowitz [21] has written extensively on the subject of pulmonary arteriosclerosis, and it is his feeling that a primary form of this disease does not exist. Ulrich [22] more recently emphasized the clinical aspects of this syndrome. In the comprehensive study of the vessels of pulmonary circulation published by Brenner [23] in 1935, the authenticity of so-called primary pulmonary sclerosis was reaffirmed and the literature reviewed. He cited 16 cases [24] and reported 1 of his own, all of which he believed could be accepted without reserve. However, the case of Bryant and White [24d] is that of generalized arteriosclerosis in an infant. The two cases of Goedel,[24e] which are almost identical with Gamma's two cases,[12] must be rejected because of extensive pulmonary thromboses. On the other hand, it is thought that Brenner's rejection of MacCallum's [25] case on the basis of "slight emphysema" is unrealistically strict in respect to the criteria of diagnosis. In 1941 Brill and Krygier [20c] reviewed the literature and presented 20 cases [26] which they thought acceptable. However, in the case of Killingsworth and Gibson [26h] there was a patent ductus arteriosus, and thus the condition must be considered a secondary type of arteriolosclerosis. In the recent literature many reported cases [27] must be excluded

20. (*a*) Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation: Part IV, Arch. Int. Med. **56**:976, 1935. (*b*) Miller, H. R.: Sclerosis of the Pulmonary Artery and Its Branches, M. Clin. North America **9**:673, 1925. (*c*) Brill, I. C., and Krygier, J. J.: Primary Pulmonary Vascular Sclerosis, Arch. Int. Med. **68**:560, 1941.

21. Moschcowitz, E.: Hypertension of the Pulmonary Circulation: Its Causes, Dynamics and Relation to Other Circulatory States, Am. J. M. Sc. **174**:388, 1927.

22. Ulrich, H. L.: The Clinical Diagnosis of Pulmonary Arteriosclerosis, Ann. Int. Med. **6**:632, 1932.

23. (*a*) Brenner.[20a] (*b*) Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation: Part I, Arch. Int. Med. **56**:211, 1935; (*c*) Part II, ibid. **56**:457, 1935; (*d*) Part III, ibid. **56**:724, 1935; (*e*) Part V, ibid. **56**:1189, 1935.

24. (*a*) Mönckberg.[7] (*b*) Ljungdahl.[9] (*c*) Ulrich.[22] (*d*) Bryant, J. H., and White, W. H.: A Case of Calcification of the Arteries and Obliterative Endarteritis, Associated with Hydronephrosis, in a Child Aged 6 Months, Guy's Hosp. Rep. **55**:17, 1901. (*e*) Goedel, A.: Zur Kenntnis der Hypertrophie des rechten Herzens und schwerer Kreislaufstörung infolge Verödung der Lungenschlagaderperipherie, Arch. path. Anat. **277**:507, 1930. (*f*) Eppinger, H., and Wagner, R.: Zur Pathologie der Lunge, Wien. Arch. inn. Med. **1**:83, 1920. (*g*) Rössle, R.: Über Hypertrophie und Organkorrelation, München. med. Wchnschr. **55**:377, 1908. (*h*) Tschistovitch, T.: Thrombo-endoartérite pulmonaire chronique, Compt. rend. Soc. biol. **89**:627, 1923. (*i*) Sanders, W. E.: Primary Pulmonary Arteriosclerosis with Hypertrophy of the Right Ventricle, Arch. Int. Med. **3**:257, 1909. (*j*) Kuntschik, R.: Zur Kenntnis der sogenannten "Primären Pulmonalsklerose," Ztschr. Kreislaufforsch. **23**:183, 1931. (*k*) Schütte, H.: Rechtsseitige Herzhypertrophie, hervorgerufen durch eine entzündliche Veränderung der kleinen Lungenarterien, Zentralbl. allg. Path. path. Anat. **25**:483, 1914. (*l*) Hart, C.: Über die isolierte Sklerose der Pulmonalarterie, Berl. klin. Wchnschr. **53**:304, 1916. (*m*) Krutzsch, G.: Über rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, Frankfurt. Ztschr. Path. **23**:247, 1920.

25. MacCallum, W. G.: Obliterative Pulmonary Arteriolosclerosis, Bull. Johns Hopkins Hosp. **49**:37, 1931.

26. (*a*) Mönckeberg.[7] (*b*) Ljungdahl.[9] (*c*) Ulrich.[22] (*d*) Brenner.[23b] (*e*) Footnote 24 *f* to *m*. (*f*) MacCallum.[25] (*g*) Cor Pulmonale, Etiology Unknown, Cabot Case 23511, New England J. Med. **217**:1045, 1937. (*h*) Killingsworth, W. P., and Gibson, S.: Primary Proliferative Pulmonary Arteriolar Sclerosis, Am. J. Dis. Child. **57**:1099, 1939.

27. Clarke, R. C.; Coombs, C. F.; Hadfield, G., and Todd, A. T.: On Certain Abnormalities, Congenital and Acquired, of the Pulmonary Artery, Quart. J. Med. **21**:51, 1927. Nagel, A.:

(Footnote continued on next page)

for similar reasons or because clinical and especially pathologic evidence was insufficient for definite diagnosis. Actually, many of the earlier reported cases are accepted on the very minimum of evidence and so could be subject to criticism by modern standards. In addition to the 17 cases of Brenner and Brill and Krygier as here modified, we have found 11 additional cases [28] that meet the standards of diagnosis. To this group we add three of our own for a total of 31 cases. In two of our cases diagnosis was made on necropsy, and in the third diagnosis was made during life by exploratory thoracotomy and lung biopsy.

REPORT OF CASES

CASE 1.—*History.*—A 26-year-old white woman (W. G. H. 250755) had an illness of 39 months' duration. Initial symptoms consisted of brief episodes of substernal pain radiating into the left chest. Three years before death she experienced progressive exertional dyspnea followed shortly by the appearance of cyanosis. Thereafter, she had orthopnea, occasional syncope, fatigue, and minimal cough, but no hemoptysis. During the last six months of illness she was confined to a bed or wheel chair. Dyspnea and cyanosis increased, and death occurred within a few hours after she lapsed into unconsciousness.

Past history revealed an allergic diathesis manifested by chronic dermatitis, hay fever, migraine, and mild asthmatic symptoms. She experienced a "streptococcal" throat infection just prior to onset of the symptoms of her final illness.

During the first year of symptoms she was observed at another hospital, where cardiac catheterization revealed pulmonary arterial hypertension (61/31 mm. Hg), identical systolic pressure in the right ventricle and pulmonary artery, no evidence of arterial blood entering the

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Über sogenannte primäre Pulmonalsklerose, Ztschr. Kreislaufforsch. **33**:620, 1941. Cheney, G.: Ayerza's Disease, with a Report of 2 Cases, Am. J. M. Sc. **174**:34, 1927. McGee, C. J., and Priest, W. S.: Pulmonary Arterial and Arteriolar Sclerosis: Report of a Case, Quart. Bull. Northwestern Univ. M. School **22**:325, 1948. Darley, W., and Doan, C. A.: Primary Pulmonary Arteriosclerosis with Polycythemia, Associated with the Chronic Ingestion of Abnormally Large Quantities of Sodium Chloride (Halophagia), Am. J. M. Sc. **191**:633, 1936. Pund, E. R., and Phinizy, T. B.: Primary Sclerosis of the Pulmonary Artery: Report of a Case, Ann. Int. Med. **5**:1391, 1932. Case Reports of the Barnes Hospital: No. 20, J. Missouri M. A. **40**:199, 1943. Wolman, M.: Hypertrophy of the Branches of the Pulmonary Artery, and Its Possible Relationships with the So-Called Primary Pulmonary Arteriosclerosis in 2 Infants with Hypertrophy of the Right Heart, Am. J. M. Sc. **220**:133, 1950. Rosenthal, S. R.: Sclerosis of the Pulmonary Artery and Arterioles: A Clinical Pathologic Entity, Arch. Path. **10**:717, 1930. Bredt, H.: Die primäre Erkrankung der Lungenschlagader in ihren verschiedenen Formen (Arteriopathia pulminalis idiogenica), Arch. path. Anat. **284**:126, 1932.

28. (*a*) Norris, R. F.: Primary Pulmonary Arteriosclerosis: Report of a Case with Marked Calcification of the Pulmonary Arteries, Bull. Johns Hopkins Hosp. **59**:143, 1936. (*b*) Taft, E. B., and Mallory, G. K.: Primary Pulmonary Vascular Sclerosis, Arch. Path. **42**:630, 1946. (*c*) Barret, A. M., and Cole, L.: Pulmonary Vascular Sclerosis with Right Ventricular Failure, Brit. Heart J. **8**:76, 1946. (*d*) Pulmonary Arteriosclerosis Severe, Arterial and Arteriolar, Cabot Case 29351, New England J. Med. **229**:408, 1943. (*e*) Seeley, H.: Primary Obliterative Pulmonary Arteriolar Sclerosis, J. A. M. A. **110**:792, 1938. (*f*) Waring, J. J., and Black, W. C.: The Syndrome of Obstruction in the Lesser Circulation, Am. J. M. Sc. **187**:652, 1934. (*g*) Sokoloff, M. J., and Stewart, H. L.: Hyperplastic Sclerosis of the Pulmonary Artery and Arterioles: Report of a Case with Discussion of the Pathogenesis, Arch. Int. Med. **51**:403, 1933. (*h*) Gilmour, J. R., and Evans, W.: Primary Pulmonary Hypertension, J. Path. & Bact. **58**:687, 1946. (*i*) Jenssen, C. F.: Pulmonalsklerose, Nord. med. **38**:802, 1948. (*j*) Spencer, H.: Primary Pulmonary Hypertension and Related Vascular Changes in the Lungs, J. Path. & Bact. **62**:75, 1950. (*k*) Bacon, C. M., and Apfelbach, C. W.: Primary Sclerosis of the Pulmonary Artery and Its Branches, Arch. Path. **3**:801, 1927.

right auricle or right ventricle, 77% oxygen saturation of the peripheral arterial blood, and cardiac output of 2.8 to 3.6 liters per minute, which was considered a low figure for the method used.

On physical examination four months prior to death, the patient was dyspneic at rest and slight cyanosis was evident on activity. There was no clubbing. Blood pressure was 105/95. Cardiac rate was 120 with a gallop rhythm. The pulmonic second sound was accentuated. There was no demonstrable cardiomegaly. No murmurs were heard. Results of examination of the lungs were entirely normal. There was no edema of the extremities. The liver was palpable 2 cm. below the right costal margin.

Roentgenogram of the chest revealed a prominent pulmonary artery, but the heart was normal and the lung fields were clear. An electrocardiogram suggested only right ventricular hypertrophy. The hemoglobin concentration was 18.2 gm. per 100 cc., and red blood cells numbered 6,500,000. Plasma and blood volumes were normal. The serological test for syphilis was negative.

Autopsy.—Gross Observations: There was cyanosis of the nail beds of the fingers, as well as of the lips and ear lobes. The fingernails presented some downward curving and increased mobility of their bases.

There was no free fluid in the peritoneal cavity. The pericardial cavity contained 50 cc. of clear yellow fluid. The heart weighed 360 gm. The right ventricular wall was markedly hypertrophied, and the right atrium was widely dilated. There was no abnormality of the valves. Their circumferences were as follows: tricuspid valve, 11.0 cm.; pulmonary valve, 7.0 cm.; mitral valve, 9.0 cm.; aortic valve, 6.0 cm. The thickness of the left ventricular musculature was 1.0 cm., while that of the right ventricle ranged from 0.4 to 1.0 cm. The coronary arteries were normal. The aorta seemed smaller than usual, as did all its major branches.

The lungs together weighed 450 gm. The pleural surfaces were smooth and glistening. On cut section the only apparent abnormality was prominence of the blood vessels. The major pulmonary vessels showed some intimal sclerosis and mucoid alteration.

The spleen weighed 200 gm. The surface was wrinkled and the pulp congested.

The liver weighed 1,050 gm. Its surface was smooth and of normal color, and an increased amount of blood exuded from the cut surface.

The right kidney weighed 150 gm., the left, 160 gm. Except for congestion these were normal.

The gall bladder, pancreas, gastrointestinal tract, adrenal gland, ureters, urinary bladder, and ovaries showed no abnormalities. The brain was not examined.

Microscopic Observations: Vessels of the heart were congested. Two larger coronary arteries presented slight to moderate intimal thickening, but there was no significant stenosis. Walls of smaller blood vessels were not thickened. A few small foci of fibrosis were present in the myocardium, but the myocardial fibers were well preserved. The mitral valve was normal.

In the lungs the most striking lesion was a generalized thickening of the walls of the arterioles, due to proliferation of intimal fibrous tissue. The arteriolar lumens in many places were markedly narrowed and in many instances appeared completely occluded (Fig. 3). Not infrequently the fibrous intimal proliferation was eccentric even to the point of polypoid intraluminal projections (Fig. 4). In sections with Mallory's aniline blue stain and in elastic-tissue-stained sections there was some irregularity in the thickness of the media, but no definite hypertrophy. Intimal reduplication of elastic tissue was frequently seen, and in places the internal elastic lamina had lost its continuity. The latter changes were also seen in medium-sized and small arteries (Fig. 5). Medium-sized and large arteries showed slight to moderate fibrous intimal thickening. No antemortem thrombi were seen in any of the sections.

Alveolar walls in most places were normal, but in places they were somewhat thickened. Some groups of alveoli were distended, others partially collapsed. Bronchi and bronchioles frequently presented an acute inflammation with polymorphonuclear leucocytes in the mucosa and muscularis and focal areas of necrosis of the epithelium. No bronchiectasis was present. A tracheobronchial lymph node was not remarkable.

The splenic sinusoids were congested, and there was moderate thickening of arterioles.

The central veins and adjacent sinusoids of the liver were distended with blood. Reticular stroma was separated from the cords of liver cells.

The adrenal parenchyma was normal. Arterioles in the adjacent tissues were normal.

The glomeruli and tubules of the kidney were well preserved. Blood vessels were congested, but there was no lesion of the arterioles.

Comment.—This case appears to fulfill the criteria of primary pulmonary arteriolosclerosis. The history of an allergic diathesis might lead to speculation as to its role in the pathogenesis. The "streptococcal" infection of the throat raises the possibility of rheumatic fever, but there was no pathologic evidence of this disease.

CASE 2.—*History.*—A 64-year-old white man (W. G. H. 270046) had a nine-month illness which began with easy fatigability, followed within two months by a nonproductive cough, episodes of precordial oppression, exertional and paroxysmal dyspnea, and orthopnea. An intervening respiratory infection was accompanied with transient chills and fever. During the fifth month of his illness, generalized anasarca developed and previous symptoms became intensified,

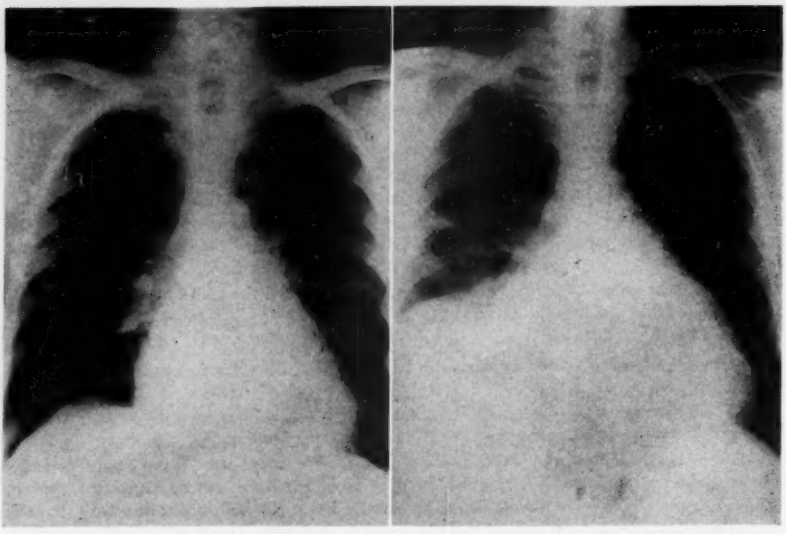

Fig. 1 (Case 2).—Left, roentgenogram of chest demonstrates cardiac silhouette suggestive of mitral valvular disease, accentuation of pulmonary arterial tree, and clear lung fields. Right, roentgenogram of chest two months later demonstrates gross cardiac enlargement and development of pleural effusion extending into the minor interlobar fissure on right.

with the appearance of cyanosis. Hospitalization and a therapeutic regimen including digitalization directed toward correction of congestive failure were only transiently successful. Thereafter, despite intensive therapy, the course was relentlessly downhill with somnolence becoming severe. Although cyanosis and dyspnea persisted, there was no further orthopnea. Coma developed, and terminally purpura became evident. There was no hemoptysis.

The past and family histories were not contributory.

On physical examination two weeks prior to death the patient was dyspneic at rest and slightly cyanotic. He was able to assume the recumbent position without increasing his dyspnea. There was also an icteric tint to the skin and sclerae. Clubbing of the fingers was not present. There was evidence of bilateral hydrothorax, but the lungs were clear with only a few subcrepitant rales at the basis. The heart was moderately enlarged. Systolic and diastolic murmurs were heard at the apex. A systolic murmur was also heard in the pulmonic area. The pulmonic second sound was accentuated. The blood pressure was 100/62. Atrial fibrillation

was present. The liver was palpable 10 cm. below the right costal border in the midclavicular line and pulsated synchronously with systole. Slight acites was present. Venous distention was evident, as was generalized edema.

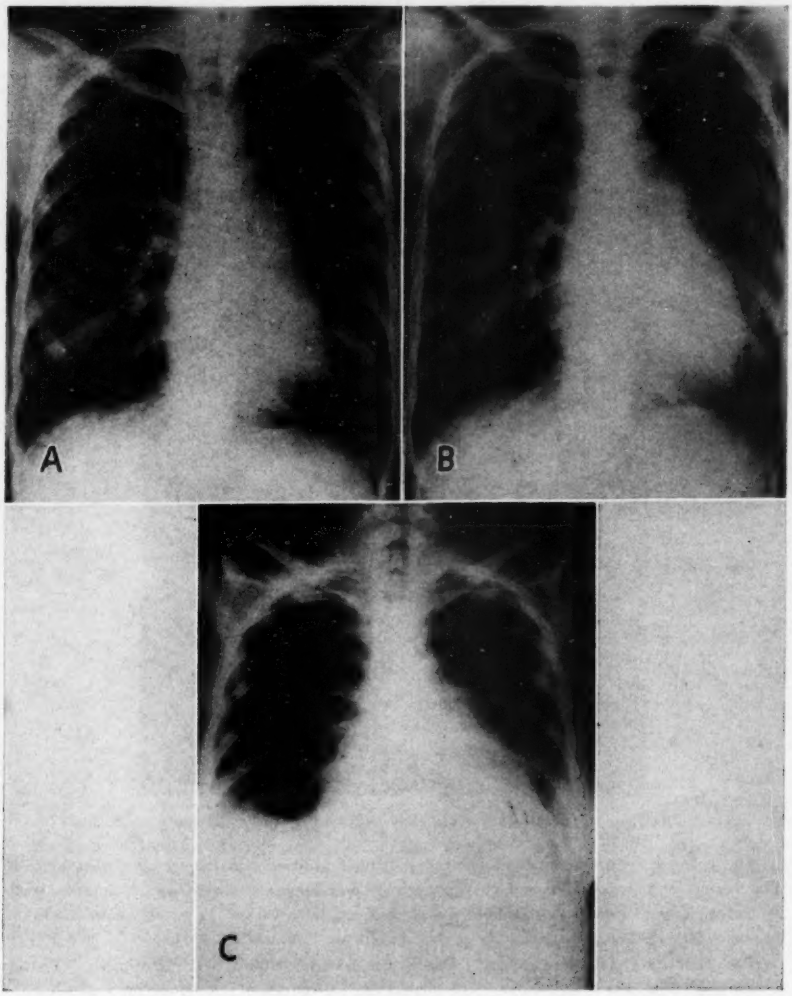

Fig. 2 (Case 3).—*A*, roentgenogram of chest demonstrates prominence of pulmonary conus and pulmonary arteries without perceptible cardiac enlargement. Lung fields are clear. *B*, follow-up study two months later demonstrates increasing cardiac enlargement. *C*, roentgenogram four months after initial study. Marked progression of cardiac enlargement, persistent accentuation of the pulmonary artery, and development of bilateral pleural effusion are evident.

A roentgenogram of the chest taken three months prior to death revealed gross enlargement of the heart, with bilateral pleural effusion, especially on the right. Two weeks later, follow-

ing intensive therapy, there was no longer evidence of pleural fluid (Fig. 1, left). The cardiac silhouette suggested left auricular enlargement. A roentgenogram made two weeks prior to death revealed recurrence of fluid in the right pleural cavity which extended into the interlobar fissure. There was generalized cardiac enlargement suggestive of pericardial effusion (Fig. 1, right). Cardiac fluoroscopy was suggestive of mitral stenosis. Electrocardiographic studies indicated right ventricular hypertrophy and the development of atrial fibrillation. The hemoglobin concentration was 17.0 gm. per 100 cc.; red blood cells numbered 6,010,000; the icterus index was 30, the prothrombin time 52% of normal, and nonprotein nitrogen 78 mg. per 100 cc. Results of urinalyses were normal except for transient reaction for albumin.

Autopsy.—Gross Observations: There was slight cyanosis of the lips and nail beds. Many small petechiae were present on the skin.

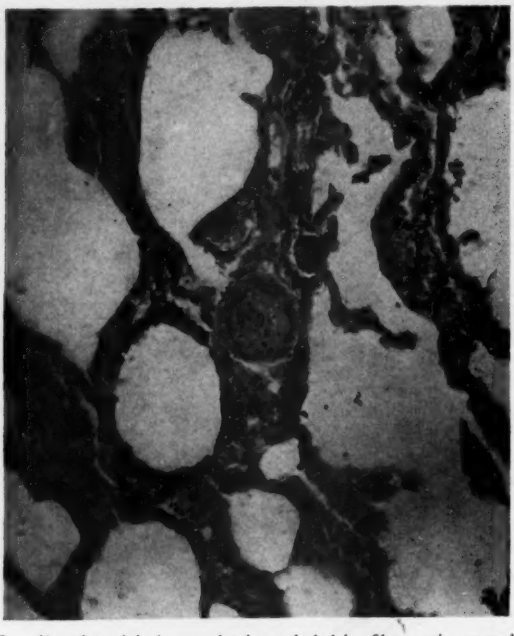

Fig. 3 (Case 1).—Arteriole is completely occluded by fibrous tissue proliferation.

The peritoneal cavity contained 100 cc. of fluid, but the peritoneal surfaces were smooth. The vessels of the omentum and gastrointestinal tract appeared congested. Numerous small hemorrhages were seen in the omentum. The liver extended 6.0 cm. below the xiphoid and 2.5 cm. below the right costal margin.

The pleural surfaces were smooth. One thousand three hundred cubic centimeters of serosanguineous fluid was found in the right pleural cavity, and 20 cc. of serous fluid was present in the left. The pericardial cavity contained 250 cc. of serosanguineous fluid, but its surfaces were smooth.

The heart weighed 500 gm. All chambers appeared enlarged, especially the right ventricle. The valve cusps and leaflets, however, showed no abnormality. An antemortem thrombus was present in the right atrial appendage. There was no congenital anomaly of the heart. Valvular circumferences were as follows: tricuspid valve, 15 cm.; pulmonic valve, 7.5 cm; mitral valve, 15 cm., and aortic valve, 7.5 cm. The coronary arteries were widely patent. The right ven-

tricular musculature measured 0.4 cm. in thickness and that of the left ventricle measured 1.5 cm. The aorta was normal except for a few atheromatous plaques.

The left lung weighed 230 gm., the right 350 gm. Each was crepitant and appeared normal.

The liver weighed 970 gm. and had a smooth capsular surface. No abnormality was noted on cut section.

The esophagus and stomach were normal. The duodenum, jejunum, ileum, and colon were filled with bloody fluid material. The mucosal surfaces were hyperemic. Also, there was diverticulosis of the sigmoid colon. The right kidney weighed 150 gm., the left 160 gm. The capsules stripped easily. The medullae were congested.

The spleen, gall bladder, pancreas, adrenal glands, ureters, urinary bladder, testes, and brain were essentially normal.

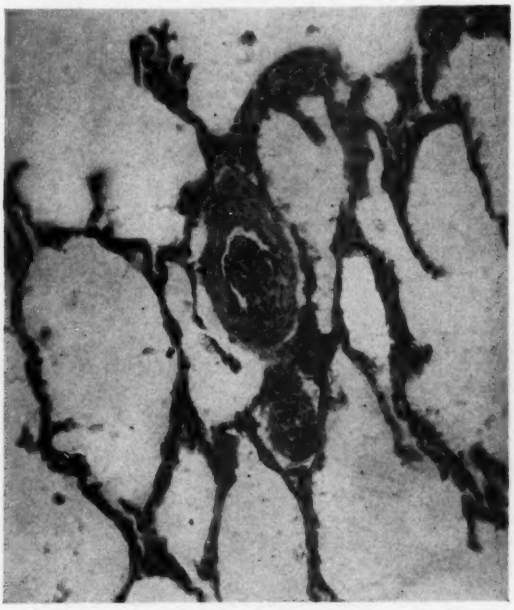

Fig. 4 (Case 1).—Intrapulmonary arteriole with intraluminal polypoid fibrous proliferation.

Microscopic Observations: The myocardial fibers were well preserved. An occasional tiny focus of myocardial fibrosis was present. Much of the thrombus in the right atrial appendage was undergoing organization, but some very recent antemortem thrombus was present. The intima of one medium-sized coronary artery was slightly thickened by fibrous tissue.

The lung sections showed the alveolar walls to be thin and uninvolved by inflammatory cells or congestion. Frequently, alveolar walls ended abruptly in small hyaline knots. The arteriolar walls were involved by severe hyaline thickening (Fig. 6), and not infrequently the lumens appeared completely closed. Small arteries presented moderate intimal thickening, and there were fragmentation and reduplication of the internal elastic lamina. Fine elastic fibers were abundant in the intimal connective tissue (Fig. 7). The media was irregularly thinned. No adventitial inflammatory cells were present. Bronchioles were normal. There was no pulmonary edema or pneumonia.

The splenic pulp was moderately congested, and splenic arterioles were moderately thickened.

The liver presented the picture of early cirrhosis. The portal connective tissue was increased in amount, and there was a moderate proliferation of bile ducts. The central portions of the

lobules showed hemorrhage with necrosis of the central liver cells. In some central areas there was an increase in fibrous tissue. Frequent bile canaliculi were distended with bile. Only a few scattered liver cells contained vacuoles of fat. The pancreas was essentially normal. The omentum showed focal hemorrhages.

In the medulla of the adrenal glands, there were several rather large collections of hematopoietic cells. Arterioles in the adjacent tissue were not thickened.

Vessels of the kidney were congested, and small hemorrhages were present in the medulla. Renal arteries presented slight intimal thickening, but the arterioles were normal.

The testes, diaphragm, and pituitary were essentially normal.

Comment.—The clinical features of interest were the severe somnolence and the total lack of orthopnea terminally. The icterus and azotemia were reflections of the severe passive con-

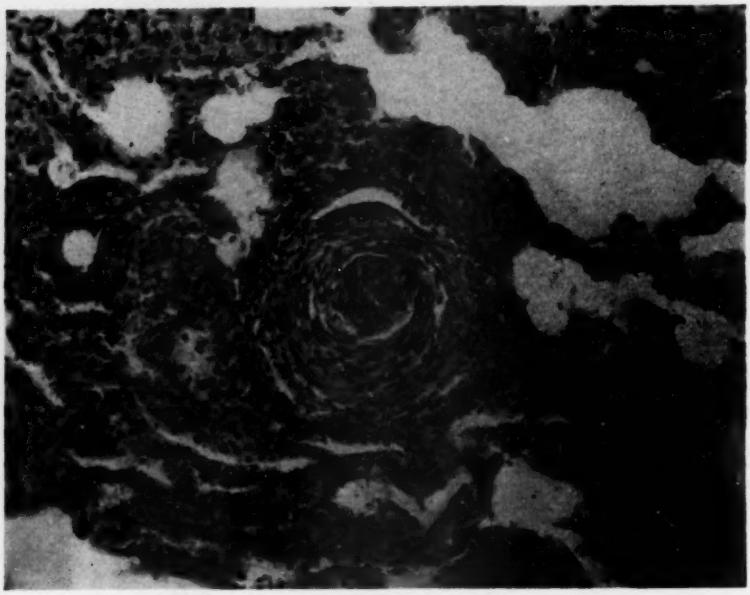

Fig. 5 (Case 1).—Small artery with marked intimal proliferation (endarteritis obliterans). Alveolar walls in this area are thickened, as compared with Figure 4. Lymphocytes are present in adventitia.

gestion that characterized the illness. Although the measurement of the right ventricular musculature was 0.4 cm., the ventricular dilatation was so great that this measurement cannot be taken as a true index of right ventricular size. The clinical impression prior to death was rheumatic heart disease with mitral stenosis and insufficiency and tricuspid insufficiency.

CASE 3.—*History.*—A 29-year-old white woman (W. G. H. 273650) was said to have exhibited symptoms of exertional dyspnea and transient cyanosis at the age of 3 years. However, she was apparently well until 10 months prior to her admission to the Wisconsin General Hospital. At that time she displayed increasing dyspnea and cyanosis, orthopnea, paroxysmal nocturnal dyspnea, weight loss, anorexia, and a chronic cough productive of moderate amounts of mucopurulent sputum. During hospitalization and therapy for congestive failure, including digitalization, she improved only transiently. Within three weeks all symptoms recurred, and hospitalization was again required. Minimal hemoptysis and some wheezing had developed in addition to the previous complaints. Again the patient improved sufficiently for minimal activity.

The past and family histories were noncontributory.

On physical examination at the time of the second hospitalization the patient was dyspneic at rest. There was definite clubbing of the fingers and toes, with cyanosis of the nail beds and lips. Examination of the lungs revealed sonorous inspiratory and expiratory rales, but very few moist rales at the bases. No cardiomegaly was demonstrable. Tachycardia (120 beats a minute) was present, and the blood pressure was 118/80. The pulmonic second sound was accentuated. A Grade II diastolic murmur was present in the pulmonic area. The liver edge was 2 cm. below the right costal margin. There was no peripheral edema.

Initially a roentgenogram of the chest revealed prominence of pulmonary vascular shadows. Otherwise the lung parenchyma was normal. The cardiac silhouette demonstrated a considerable

Fig. 6 (Case 2).—Two arterioles whose lumens are nearly occluded by dense fibrous tissue. Alveolar walls are thin but frequently end abruptly in hyaline knots.

enlargement of the pulmonary artery-conus segment (Fig. 2*A*). Roentgenographic examination on the second hospital admission gave similar findings, except for appreciable increase in the cardiac silhouette (Fig 2*B*). Angiocardiography did not reveal a right-to-left shunt and demonstrated a distinct enlargement of the right auricle and right ventricle, as well as marked enlargement of the main pulmonary artery. An electrocardiogram indicated right ventricular hypertrophy. The hemoglobin concentration was 24 gm.; red blood cells numbered 7,100,000, and the hematocrit was 73%. Urinalyses showed no abnormalities except for minimal transient positive reaction for albumin. A serological test for syphilis was negative. The vital capacity was 72% of normal.

Exploratory thoracotomy was performed in order to rule out a surgically correctible disease and to establish a diagnosis. The right atrium was dilated, and there was marked hypertrophy of the right ventricle. The left atrium and left ventricle were normal. The pulmonary artery

was very large, measuring 4.25 cm. in diameter. There was no evidence of patent ductus arteriosus. The pressure in the pulmonary artery was measured at 62 cm. of water, and this was the maximum reading for the manometer available at the operation. A biopsy specimen of the lingula was obtained.

The patient was again seen five months after her first admission. During the previous three weeks she had had evidence of right-heart failure with pitting edema of the legs and abdomen, ascites, and pleural effusion. The cough had almost entirely disappeared. There had been no further hemoptysis. Cyanosis had not progressed. She was not dyspneic at rest, though minimal exertion produced prompt dyspnea.

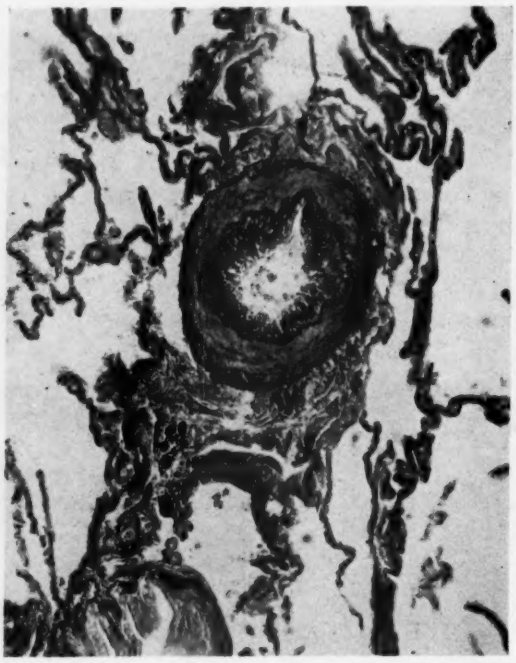

Fig. 7 (Case 2).—Internal elastic lamina is slightly fragmented, and many fine elastic fibrils penetrate thickened intima. Normal bronchiole is present at one edge of section. Elastic-tissue stain.

Physical findings were those of right ventricular failure. A small pleural effusion was demonstrated on the right, but there were only a few rales present. Examination revealed a definite cardiomegaly, a diastolic murmur in the pulmonic area with an accentuated pulmonic second sound, and a palpable pulmonic shock. A Grade II localized apical systolic murmur had also developed. Cardiac rate was 108. Blood pressure was 112/93 in the right arm and 144/115 in the right leg.

A roentgenogram revealed the heart to have enlarged (Fig. 2C), and small pleural effusions were evident bilaterally. Studies again showed polycythemia. Alkali reserve was 20.8 mEq. per liter. Total serum proteins were 4.0 gm. per 100 cc., with 2.6 gm. of albumin. Cholesterol was 230 mg. per 100 cc. An arm-to-tongue circulation time using dehydrocholic acid (decholin®) was 25 seconds. An arm-to-lung circulation time using ether precipitated peripheral vascular collapse, rapidly developing coma, a convulsive seizure, and death within 20 minutes despite all efforts to sustain the patient. Postmortem examination was not permitted.

Surgical Pathology.—Microscopic Observations: The walls of arterioles and small arteries were moderately to markedly thickened, owing to an increase of intimal fibrocollagenous tissue. Walls of arterioles were hyalinized, and thickening was sometimes so marked as to nearly close the lumen (Fig. 8). The lumens of small arteries were occasionally eccentric in position, owing to the fibrous intimal proliferation (Fig. 9). In the elastic-tissue-stained sections, the internal elastic lamina showed reduplication, and fine elastic fibrils penetrated the thickened intima. No definite changes in the muscular walls of the small arteries were noted. A small number of scattered lymphocytes was present in the periarterial and peribronchiolar connective tissue.

The alveolar walls in general were thin and delicate, but not infrequently alveolar walls ended abruptly in small hyaline knots. The pleural surface was normal. Bronchioles and alveoli contained no exudate.

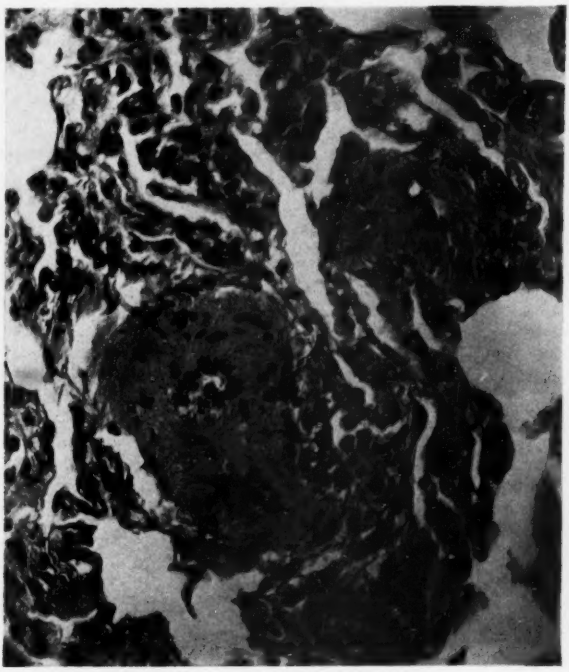

Fig. 8 (Case 3).—Marked hyaline thickening of an arteriole. Lumen is nearly occluded.

Comment.—The mode of this patient's death suggests that these patients are particularly vulnerable to ether. Perhaps its use should be contraindicated for patients in whom this disease is suspected.

It is indeed unfortunate that permission for autopsy could not be obtained. Exploratory thoracotomy was of great value in eliminating certain known causes of pulmonary arteriolosclerosis. The angiocardiogram was also of value, in a negative way, as it eliminated the likelihood of an interauricular or interventricular septal defect. Nevertheless, these were no adequate substitute for detailed autopsy examination.

In the absence of a cause for the pulmonary arteriolar lesion, we believe that this, in all probability, is a case of primary pulmonary arteriolosclerosis. To our knowledge this is the first case reported in which exploratory thoracotomy and lung biopsy were utilized to establish the diagnosis of this disease.

INCIDENCE

The incidence of sclerosis of the larger pulmonary arteries and arterioles is relatively high and, as in systemic arteriosclerosis, seems to be proportional to age. Ljungdahl [9] and Brenner [23b] both found evidences of sclerosis in more than 90 and 65%, respectively, of all autopsies. However, their criteria were liberal. Perhaps more representative are the figures of 7.4% in 800 routine autopsies given by Miller [20b] and 6.5% in 770 routine autopsies given by Moschowitz.[21]

The incidence of primary pulmonary arteriolosclerosis, however, is very low. Seely [28c] found the ratio 1:3,800 autopsies at the New Haven Hospital and Mac-

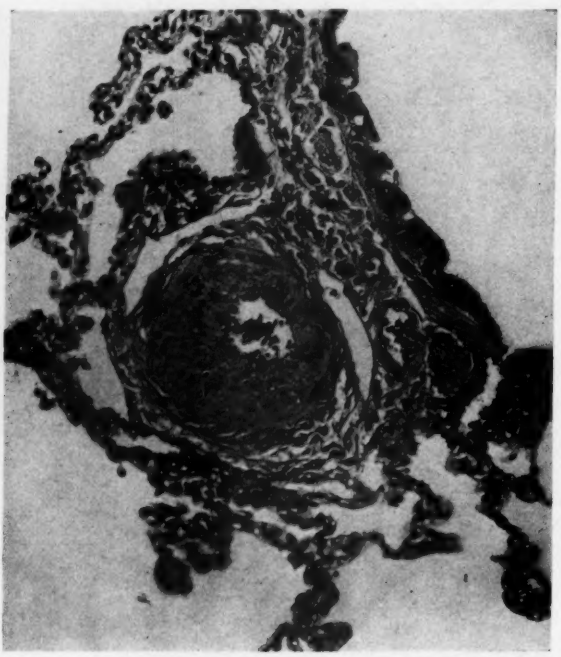

Fig. 9 (Case 3).—Small muscular artery with moderate fibrous intimal thickening and eccentric position of lumen. Adjacent bronchiole and alveolar walls are normal.

Callum [25] only 1:12,000 autopsies at Johns Hopkins Hospital. More recently Jenssen [28i] reported an incidence of 1:1,860 over a 10-year period. Review of Wisconsin General Hospital autopsy records over the past 26-year period discloses an incidence of 2 cases in 5,991 autopsies.

CAUSATION

As is usually the case with diseases of unknown cause, numerous etiological theories have been offered for primary pulmonary arteriolosclerosis. Most have their corollary in the theories that have been advanced to explain systemic arteriosclerosis. Most investigators have considered that pulmonary hypertension was the mechanism

responsible and likened the arteriolar changes to those found in the arteriolonephrosclerosis of systemic hypertension.[29]

When one examines the basic pathophysiology of the diseases that produce the secondary form of pulmonary arteriolosclerosis, it becomes evident that the production of a hypertension in the lesser circulation is indeed a frequent denominator. The hypertension may be produced by many different mechanisms. Although previously pulmonary hypertension was in the main theoretical, cardiac catheterization has made it possible to substantiate this by direct measure. Thus, Bloomfield and associates,[30] Borden and co-workers,[31] and Dexter and colleagues [32] have demonstrated the presence of pulmonary hypertension in varied cardiovascular and/or pulmonary diseases. Cournand [33] has also shown in the normal person that deep breathing and intermittent pressure breathing, by increasing the intra-alveolar pressure, increase pulmonary arterial pressure. Hamilton and others [34] have similarly demonstrated that intra-alveolar pressure variations are effective temporarily in creating marked variation in pulmonary vascular resistance. These studies clarify the work of Smith and associates,[35] who produced pulmonary arteriolosclerosis by allowing animals to be subjected to increased oxygen tension and increased barometric pressure. This work was later modified by Rehbock, Oldt, and Dixon [36] to show that the increased oxygen tension was not the responsible factor. The probable mechanism responsible was an increase in intra-alveolar tension, producing a sustained pulmonary hypertension which, in turn, was the prime factor in the development of the pulmonary arteriolosclerosis.

Although pulmonary arteriolosclerosis is occasionally found in association with certain congenital cardiovascular lesions in which pulmonary blood flow is known to be increased, notably patent ductus arteriosus and interatrial septal defect, it is relatively uncommon. From a correlative standpoint the occurrence of pulmonary arteriolosclerosis more closely parallels the incidence of pulmonary hypertension,

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29. Brill and Krygier.[20c] Taft and Mallory.[28b]

30. Bloomfield, R. A.; Lauson, H. D.; Cournand, A.; Breed, E. S., and Richards, D. W., Jr.: Recording of Right Heart Pressures in Normal Subjects and in Patients with Chronic Pulmonary Disease and Various Types of Cardio-Circulatory Disease, J. Clin. Invest. **25**:639, 1946.

31. Borden, C. W.; Wilson, R. H.; Ebert, R. V., and Wells, H. S.: Pulmonary Hypertension in Chronic Pulmonary Emphysema, Am. J. Med. **8**:701, 1950.

32. Dexter, L.; Haynes, F. W.; Burwell, C. S.; Eppinger, E. C.; Sogeston, R. P., and Evans, J. M.: Studies of Congenital Heart Disease: II. The Pressure and Oxygen Content of Blood in the Right Auricle, Right Ventricle, and Pulmonary Artery in Control Patients, with Observations on the Oxygen Saturation and Source of Pulmonary "Capillary" Blood, J. Clin. Invest. **26**:554, 1947.

33. Cournand, A.: Recent Observations on the Dynamics of the Pulmonary Circulation, Bull. New York Acad. Med. **23**:27, 1947.

34. Hamilton, W. F.; Woodbury, R. A., and Vogt, E.: Differential Pressures in the Lesser Circulation in the Unanesthetized Dog, Am. J. Physiol. **125**:130, 1939.

35. Smith, F. J. C.; Bennett, G. A.; Heim, J. W.; Thomson, R. M., and Dinker, C. K.: Morphological Changes in the Lungs of Rats Living Under Compressed Air Conditions, J. Exper. Med. **56**:79, 1932.

36. Rehbock, D. J.; Oldt, M. R., and Dixon, H. M.: Effect of Exposure to High Oxygen Tension on the Lungs and Heart of the Rat, Arch. Path. **30**:1172, 1940.

which has been shown by Dexter and co-authors [37] and Cournand [38] to be infrequent in these pathologic states. The exact role played by an increase in pulmonary blood flow in the development of pulmonary arteriolosclerosis remains to be evaluated.

Despite the evidence that has accumulated to support the contention that hypertension is the important etiological factor, there are still many instances of pulmonary arteriolosclerosis in which hypertension is known not to exist. It is suggested, then, that hypertension may not be the basic cause of pulmonary arteriolosclerosis. Further understanding of the problem of pulmonary hypertension was offered by the studies of Logaras [38] and von Euler.[39] These have shown that pulmonary artery pressure is increased markedly when there is a decrease in pulmonary alveolar oxygen tension. Similarly, Motley and colleagues [40] have demonstrated marked pulmonary hypertension with normal systemic pressures on low oxygen breathing. This recent work gives one explanation for the older observations of Hurtado,[41] who found rather marked degrees of pulmonary arteriosclerosis in natives of the Peruvian Andes, and Campbell,[42] who produced pulmonary arteriolosclerosis in cats by subjecting them to an environment of low oxygen tension for prolonged periods. Evidence to date permits no definite conclusions concerning the mechanism by which hypoxia alone causes a sustained hypertension of the lesser circulation. Cournand [43] has, however, indicated the importance of hypoxia and pulmonary hypertension as interrelated factors in the mechanism leading to both low- and high-output cardiac failure in chronic pulmonary disease.

Our attention, therefore, is directed toward the role of hypoxia in the production of arteriosclerosis. Hueper [44] emphasized the importance of hypoxia in the etiology of arteriosclerosis. In brief, he believed that anoxemia may serve to produce arteriosclerosis through the operation of four main etiological factors. These he listed as abnormal vasotonia; increased and decreased intravascular hydrostatic pressure; colloidal plasmatic instability, and, finally, hematic anoxemia. This theory offers a plausible explanation for all causes of secondary pulmonary arteriosclerosis.

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37. Dexter, L.; Haynes, F. W.; Burwell, C. S.; Eppinger, E. C.; Sosman, M. C., and Evans, J. M.: Studies of Congenital Heart Disease: III. Venous Catheterization as a Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy of Fallot, Ventricular Septal Defect and Auricular Septal Defect, J. Clin. Invest. **26**:561, 1947.

38. Logaras, G.: Further Studies of the Pulmonary Arterial Blood Pressure, Acta physiol. scandinav. **14**:120, 1947.

39. von Euler, U. S., and Liljestrand, G.: Observations on the Pulmonary Arterial Blood Pressure in the Cat, Acta physiol. scandinav. **12**:301, 1947.

40. Motley, H. L.; Cournand, A.; Werko, L.; Himmelstein, A., and Dresdale, D.: The Influence of Short Periods of Induced Acute Anoxia upon Pulmonary Artery Pressures in Man, Am. J. Physiol. **150**:315, 1947.

41. Hurtado, A.: Unpublished data, cited by McCann, W. S.: The Ayerza Syndrome, Proc. Internat. Assemb. Inter-State Post-Grad. M. A. North America **7**:83, 1931.

42. Campbell, J. A.: Further Observations on Oxygen Acclimatisation, J. Physiol. **63**:325, 1927.

43. Cournand, A.: Some Aspects of the Pulmonary Circulation in Normal Man and in Chronic Cardiopulmonary Disease: The Fourth Walter Wile Hamburger Memorial Lecture, Institute of Medicine of Chicago, Circulation **2**:641, 1950.

44. Hueper, W. C.: Arteriosclerosis, Arch. Path. **38**:162, 245, and 350, 1944; **39**:51, 117, and 187, 1945.

The etiology of primary pulmonary arteriolosclerosis, however, remains in doubt. Brenner felt that right cardiac hypertrophy and pulmonary arteriolosclerosis were independent of each other and were due to a common cause, but he did not speculate on the common causation. Gilmour and Evans [28h] described this disease under the title "primary pulmonary hypertension." They considered the cause to be a hypoplasia (developmental defect) of the arterioles. Spencer,[28j] as well as Barret and Cole,[28c] postulated that pulmonary hypertension was the etiological factor in the production of the arteriolosclerosis. In this regard it is of interest to refer to the papers of De Navasquez [45] and East,[46] who present cases in which hypertrophy of the right ventricle was the only significant finding, and, although pulmonary artery pressure apparently was not measured, they felt that a primary hypertensive process within the lesser circulation was the responsible factor. These authors found no significant degree of pulmonary arteriolosclerosis in the five cases in which microscopic examination was made.

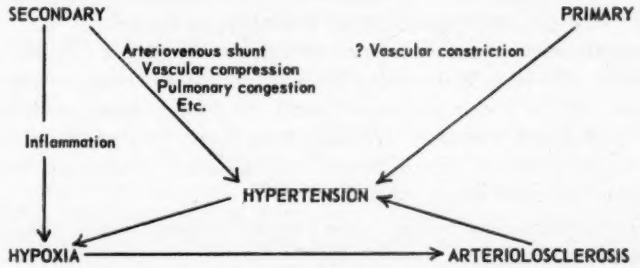

Fig. 10.—Pathogenesis of pulmonary arteriolosclerosis.

A final observation in regard to hypertension is worthy of note. Studies on patients with systemic essential hypertension have failed to reveal hypertension of the pulmonary circulation.[47] It is also evident that patients with primary pulmonary arteriolosclerosis do not have systemic hypertension. This suggests that the so-called essential hypertensions in the systemic and pulmonary circulations have little in common other than an unknown causation.

One may conclude from the evidence that has been presented that pulmonary arteriolosclerosis may result from hypoxia and that the usual cause of this hypoxia is a pulmonary hypertension. In the case of primary pulmonary arteriolosclerosis, an essential hypertension confined to the pulmonary circuit may be responsible for the arteriolar lesions. Once the processes of hypertension and pulmonary arteriolosclerosis become manifest, a vicious circle is established, one process serving to perpetuate and increase the other.

With the theory thus proposed (Fig. 10), it is possible that the entity of primary pulmonary arteriolosclerosis could be a misnomer and that it might be more correct to refer to the disease as "primary pulmonary hypertension." However, before one

45. De Navasquez, S.; Forbes, J. R., and Holling, H. E.: Right Ventricular Hypertrophy of Unknown Origin: So-Called Pulmonary Hypertension, Brit. Heart J. **2**:177, 1940.

46. East, T.: Pulmonary Hypertension, Brit. Heart J. **2**:189, 1940.

47. Dexter and others.[32] Cournand.[33]

is justified in using this term, it must be shown by measurement that the pulmonary arterial blood pressure is elevated in the absence of significant anatomic pulmonary arteriolar change or cardiac enlargement. Further, it must be shown that these two lesions develop as secondary phenomena. Thus recognizing the present limitations in our knowledge, we can but adhere to the time-honored term primary pulmonary arteriolosclerosis and present the evidence available.

CLINICAL PICTURE

The clinical picture of primary pulmonary arteriolosclerosis has been frequently described, but often without reference to previous cases. In earlier literature emphasis was placed on the pathology, and clinical descriptions frequently were meager. In the first part of this century the wastebasket term "Ayerza's disease" became popular and served as a convenient label for almost every disease presenting the complex of cor pulmonale, severe cyanosis, and speculated or actual disease of the pulmonary vessels, irrespective of the causation. This term retains its adherents today despite the efforts of numerous writers to discourage its use.

An analysis of the cases of the primary form of arteriolosclerosis (Tables 1 and 2) has presented us with a fairly clear clinical picture. It has been recognized that characteristically this disease progresses through two distinct phases. Initially symptoms are predominantly those of respiratory insufficiency; but, as the disease progresses, the characteristic picture shifts to one of cardiac insufficiency manifested primarily by right-heart failure.

Dyspnea is usually the first and most constant symptom of this disease, being present in all reported cases. Initially dyspnea occurs only on exertion, but as the disease progresses it finally becomes evident even at rest. It is this symptom that usually serves to focus attention on the respiratory system. In the later phase of the disease chemical changes in the blood, by acting on chemoreceptors, may be in part responsible for the dyspnea, but initially it is possible that dyspnea is the result of pressoreceptors within the lesser circulation. An increase of pressure within these vessels has been shown to increase the rate and volume of respiration.[48]

Although orthopnea is encountered sporadically throughout the course of the disease, we have been impressed with its inconstancy. The ability of these patients, though dyspneic and cyanotic at rest, to assume recumbency without increased discomfort may be striking. Cough is a frequent symptom. Occasionally, features of an asthmatic type of bronchitis may appear, but true asthma is not evident. Sputum may be moderately abundant and mucoid to mucopurulent. Hemoptysis was a feature in six of the cases studied; in one case, extensive pulmonary hemorrhage was the presenting complaint.

Although cyanosis has been emphasized as the one outstanding clinical feature, it actually may be minimal. This was true in the cases we observed. However, despite its variable intensity, it has been a constant feature of all recorded cases.

48. Harrison, T. R.; Harrison, W. G.; Calhoun, J. A., and Marsh, J. P.: Congestive Heart Failure: XVII. The Mechanism of Dyspnea on Exertion, Arch. Int. Med. **50**:690, 1932. Megibow, R. S.; Katz, L. N., and Feinstein, M.: Kinetics of Respiration in Experimental Pulmonary Embolism, ibid. **71**:536, 1943.

Through the mechanism of decreased arterial blood oxygen saturation, as well as through compensatory increase in hemoglobin concentration, cyanosis may be explained.

The presenting symptoms, then, are dyspnea, cough, hemoptysis, and cyanosis. In this phase, pulmonary hypertension has developed and there is pulmonary arteriolosclerosis; but there is not, as yet, an overwhelming work load on the cardiac musculature. Finally, decompensation does ensue, and its signs and symptoms are then superimposed on the preexisting clinical picture. The resultant picture is best described clinically as that of right-heart failure with venous distention, progressive peripheral edema, passive congestion, and development of effusions in the pleural, peritoneal, and pericardial cavities. The absence of pulmonary congestion in the presence of obvious cardiac failure is striking. The lung fields characteristically remain relatively clear of rales. The absence of pulmonary congestion has led many writers to feel that this, more than any other finding, is of paramount diagnostic significance. Hydrothorax was a feature of the disease in one-third of the cases, despite the absence of pulmonary congestion or other evidence of left ventricular failure. This is probably due to the fact that the venous return of the parietal pleurae is by way of the azygos vein, which enters the caval vein of the failing right heart.

Initially physical findings are minimal, and frequently cyanosis is all that is evident. Clubbing of the fingers and toes, though encountered, is not common. Cardiac examination early may reveal an accentuated pulmonic second sound and occasionally a pulmonic systolic murmur. As the disease progresses, right ventricular hypertrophy becomes evident. Closure of the pulmonic valves may become easily palpable. Pulmonic systolic and precordial systolic murmurs may become more pronounced. With increasing dilatation of the pulmonary artery, relative pulmonary incompetency may produce a diastolic murmur. Systemic blood-pressure determinations were normal in almost all cases.

Other less characteristic features of the clinical picture of this disease have been described. Of these, pain similar to angina pectoris was encountered sufficiently often (11 cases) to attract considerable attention. This may be a manifestation of coronary insufficiency, but early clinicians believed that this type of pain was peculiar to the disease and referred to it as "hypercyanotic angina." They considered the pain to originate within the pulmonary arteries. Disturbances of cardiac rhythm have been described infrequently. Hoarseness has been emphasized by Ulrich [22] and ascribed to pressure on the recurrent laryngeal nerve. Syncopal attacks, though rare, do occur and can be ascribed to cerebral hypoxia. Somnolence was severe in one of our patients (Case 2), but this symptom was reported in only two other cases. Previous authors have drawn attention to the youthfulness of the patients. However, nine of the patients listed in Table 1 were more than 40 years old. There is no significant sex predominance. Only one patient was a Negro. Great variability has been reported in the duration of symptoms in this disease. One patient had symptoms for only one month, whereas at the other extreme symptoms were present for as long as 26 years. However, it is likely that duration of symptoms is only a rough guide to the duration of the underlying pathologic process.

Routine laboratory studies were of little aid in establishing the diagnosis. There is frequently a compensatory polycythemia. Of 18 cases in which the red blood cell

TABLE 1.—*Primary Pulmonary Arteriolosclerosis*

Author; Date	Sex; Age	Dyspnea	Orthopnea	Precordial Pain	Cyanosis	Peripheral Edema	Hemoptysis	Murmurs	P_2 Accentuated	Hemoglobin, Gm./100 Cc.	R. B. C., Millions	Serologic Reaction	Electrocardiogram†	Roentgenogram‡	Duration of Symptoms	Ventricular Hypertrophy, Cm. Right	Ventricular Hypertrophy, Cm. Left	Heart Weight, Gm.	Atherosclerosis of Aorta	Atherosclerosis of Main Pulmonary Artery	Ascites, Hydrothorax, and/or Hydropericardium§	Clinical Diagnosis
Clinical and Pathologic Data*																						
Mönckeberg, 1907 [7]	F; 33	..	.	..	+	+	..	Apical syst. and diast.	..	....	...	..	.....	....	4 mo.	+	0	...	0	+	P	.....
Rössle (Case 2), 1908 [24g]	F; 20	+	..	..	..	..	..	....	..	....	...	..	.....	....	? yr.	+	0	...	0	0	.....	Congenital heart disease
Sanders, 1909 [24i]	M; 33	..	..	..	..	..	..	....	..	....	...	..	.....	....	....	+	0	...	+	+	0	Heart disease
Schütte, 1914 [24k]	F; 74	..	..	..	..	+	..	....	..	....	...	..	.....	....	....	+	0	...	+	..	A; H	Cardiac insufficiency
Ljungdahl, 1915 [9]	F; 36	+	..	..	+	+	..	Pulmon. syst. and diast.	0	....	...	..	.....	....	....	0.8	1.2	...	..	+	A	.....
Hart (Case 1), 1916 [24l]	F; 30	+	..	..	+	+	..	+	..	....	...	..	.....	....	..	+	0	..	+	+	.....	Myocardial fibrosis
Hart (Case 2), 1916 [24l]	F; 25	+	..	..	+	+	..	Apical and pulmon. syst. and diast.	..	....	...	..	.....	....	....	+	0	.	0	+	P; A; H	Mitral stenosis
Krutzsch (Case 1), 1920 [24m]	M; 26	..	..	..	..	+	..	....	..	....	...	..	.....	....	....	1.2	1.1	..	0	+	A; H	.....
Krutzsch (Case 2), 1920 [24m]	M; 23	..	..	..	..	0	..	....	..	....	...	..	.....	....	....	0.9	1.0	...	+	+	A; H; P	.....
Eppinger and Wagner, 1920 [24f]	M; 50	+	..	..	+	+	..	....	+	....	6.2	..	.....	R	....	1.0	1.0	...	0	0	.....	Primary pulmonary arteriosclerosis
Tschistovitch, 1923 [24h]	F; 38	+	..	..	+	+	..	0	..	....	...	..	.....	....	3 yr.	+	..	...	..	..	.....	Emphysema
Bacon and Apfelbach, 1927 [28k]	F; 40	+	..	+	+	+	..	Apical	+	85%	6.08	..	RAD	R; L	5 yr.	0.7	0	330	+	+	A	Mitral disease
Kuntschik, 1931 [24j]	F; 15	+	..	..	+	..	+	....	..	....	...	..	.....	....	5 yr.	1.4	0.7	....	0	+	.....	Tuberculosis
MacCallum, 1931 [28]	F; 39	+	..	+	+	+	..	Apical syst. and diast.	+	104%	6.2	—	RAD	....	4 mo.	0.8	1.2	390	0	+	0	.....
Ulrich, 1932 [22]	F; 31	+	..	+	+	+	+	Syst.	..	....	...	—	RAD	R; PA	4 yr.	+	..	425	..	+	A	Congenital heart disease
Sokoloff and Stewart, 1933 [28g]	M; 48	+	..	+	+	+	+	....	+	85%	5.2	—	.....	R; PA	10 yr.	+	..	530	0	+	A; H; P	Primary pulmonary sclerosis
Waring and Black, 1934 [28f]	M; 38	+	..	..	+	+	..	Diast.	..	115%	7.25	—	RAD	....	"Many yr."	0.8	..	...	0	0	.....	.....
Brenner (Case 1), 1935 [28b]	M; 11	+	..	+	+	0	..	Pulmon. syst.	+	....	...	—	RAD	PA	3 yr.	1.5	1.2	305	+	+	0	Patent ductus arteriosus

Norris, 1936 [28a]	M; 35	+	..	0	+	+	0	Syst. and diast.	..	16	4.98	—	RAD	R; PA	1 yr.	1.3	1.5	530	+	+	A	Congenital heart disease
Cabot Case 23511, 1937 [28g]	M; 10	+	+	..	+	+	+	0	+	75%	4.6	..	RAD	R	2 yr.	+	0	...	..	..	.....	Congenital heart disease
Seeley, 1938 [28e]	F; 68	+	+	..	+	+	..	Apical syst.	..	91%	6.2	—	RAD	....	1 mo.	0.9	1.1	390	+	+	A; H	.....
Brill and Krygier, 1941 [28c]	F; 21	+	+	+	+	0	+	0	+	122%	5.7	—	RVS	R; L; PA	2 yr.	0.7	0.7	690	0	+	A	Primary pulmonary sclerosis
Cabot Case 29351, 1943 [28d]	M; 54	+	+	..	0	+	+	0	0	16	5.15	—	AF	R	12 yr.	0.7	0	750	..	+	0	Arteriosclerotic heart disease
Gilmour and Evans, 1946 [28b]	F; 44	+	+	+	+	+	..	0	..	115%	5.9	..	RAD	R	2 yr.	0.7	0	360	+	+	.....	Primary pulmonary arteriosclerosis
Barret and Cole, 1946 [28c]	M; 34	+	0	..	+	+	..	0	+	112%	5.6	—	RAD	R; PA	4 mo.	0.8	1.4	455	+	+	A; H	.....
Taft and Mallory, 1946 [28b]	F; 56	+	..	+	+	+	..	0	..	14.2	5.17	—	RAD	R; PA	5 mo.	0.7	..	280	..	+	H	Raynaud's disease of lungs
Jenssen, 1948 [28i]	M; 48	+	..	+	+	+	..	Syst.	+	112%	5.58	—	RAD	R	6 yr.	0.7	0	540	0	0	A; H	Heart failure
Spencer (Case 1), 1950 [28j]	F; 22	+	..	+	+	0	..	Pulmon. syst.	..	105%	5.4	..	.....	....	4 wk.	0.6	0	...	0	+	H	.....
Parmley and Jones (Case 1), 1951	F; 28	+	+	+	+	0	0	0	+	18.2	6.5	—	RVS	L	27 mo.	1.0	1.0	360	0	+	0	Primary pulmonary arteriosclerosis
Parmley and Jones (Case 2), 1951	M; 64	+	+	+	+	+	0	Apical syst. and diast.	+	17.0	6.01	—	RAD; AF	R	9 mo.	0.4	1.5	500	+	0	A; H; P	Rheumatic heart disease
Parmley and Jones (Case 3), 1951	F; 29	+	+	0	+	+	+	Pulmon. diast.	+	24.0	7.10	—	RVS	R; PA	26? yr.	..	..	...	.	..	A; H	Primary pulmonary arteriosclerosis

* Plus sign indicates presence of abnormality; minus sign, negative reaction or normal; zero, absence of sign; leaders, information not given.
† RAD is right axis deviation; RVS, right ventricular strain; AF, auricular fibrillation.
‡ R means heart enlarged to right; L, lung fields clear; PA prominent pulmonary artery or conus.
§ A means ascites; H, hydrothorax, and P, hydropericardium.

count or hemoglobin concentration was recorded, one or the other was significantly elevated in 13. A negative serological test for syphilis is important.

The studies that are of diagnostic importance include those that evaluate intracardiac dynamics and structure. In this respect angiocardiography is helpful, but cardiac catheterization is the procedure of choice. An increased right ventricular or pulmonary artery pressure is to be expected. If the diagnosis is suspected, an exploratory thoracotomy with biopsy of the lung to demonstrate the arteriolar lesion should be considered. Pulmonary artery pressures may be measured directly, and direct visualization of the heart will enable the isolated right ventricular enlargement to be fully evaluated. At the same time, any other disease may be ruled out or corrected if surgically possible.

Roentgenographically the earliest indication of this disease is that of an accentuated pulmonary conus-artery segment. Eight of the 16 cases in which results of

TABLE 2.—*Summary of Symptoms and Signs Reported in Twenty-Five Cases with a Clinical Record*

Sign or Symptom	No. of Cases	Percentage
Dyspnea	25	100
Cyanosis	25	100
Cardiomegaly	21	84
Peripheral edema	20	80
Hepatomegaly	13	50
Precordial pain	11	44
Orthopnea	7	28
Hemoptysis	7	28
Somnolence	3	12
Clubbing	2	8

roentgenographic examination were recorded presented this finding. Later, right ventricular hypertrophy may develop. The rapidity of this development is demonstrated in the series of roentgenograms taken in Case 3 (Fig. 2). In reviewing the films obtained in Case 2 (Fig. 1), one can see that the anteroposterior cardiac silhouette may be nonspecific or suggestive of mitral valvular disease. Lateral and oblique views, as well as fluoroscopy, are required to demonstrate clearly the isolated right ventricular hypertrophy. Terminally pericardial effusion may be the predominant finding. Aside from the frequent development of pleural effusion, the lung fields remain clear except for the accentuation of the pulmonary arteries. The electrocardiogram may be of diagnostic aid. There is no characteristic pattern produced, however. Almost uniformly the tracing is one of right ventricular hypertrophy.

There is no specific therapy for this disease. All therapeutic efforts directed toward control of pulmonary infection or cardiac failure have been of only transient benefit.

PATHOLOGY

Gross Observations.—The macroscopic findings in our cases and in the cases culled from the literature are summarized in Table 1. In order to justify a diagnosis of primary pulmonary arteriolosclerosis, all the factors now known to cause secondary arteriolosclerosis must be absent. This makes the diagnosis of primary pulmonary arteriolosclerosis one of exclusion. Specific inflammation, particularly syphilis and rheumatic fever, must be excluded.

The findings at autopsy include evidence of congestion secondary to right-heart failure. Hypertrophy and dilatation of the right ventricle without significant enlargement of the left were present in all the cases. The lungs frequently appeared normal. Even pulmonary congestion was usually conspicuous by its absence. Pulmonary edema was absent in all but one case.[28h] The pulmonary vessels have been described as thickened and prominent on the cut surface. In many cases reported the main pulmonary artery was dilated; in contrast, the pulmonary veins were small.

The clinical and pathologic features of this disease may be closely simulated by embolic occlusion of the pulmonary arteries. In many cases a decision as to which disease process is basic may be very difficult. Indeed, primary pulmonary arteriolosclerosis and multiple occlusive pulmonary thrombi of embolic origin may coexist in the same patient. It is known that thickening of smaller vessels occurs distal to a thrombus in a pulmonary artery, and certainly pulmonary embolism might be expected in cases of primary pulmonary arteriolosclerosis with peripheral venous congestion. Nevertheless, in most of the reported cases and in our two cases with autopsy, no thrombi were present in any of the larger pulmonary arteries. We feel that the presence of large occlusive or partially occlusive thrombi in the large pulmonary arteries should mitigate against the diagnosis of primary pulmonary arteriolosclerosis, especially if peripheral veins also contain antemortem thrombi.

Microscopic Observations.—The lungs were the site of the significant microscopic pathology, and the other organs were free of any disease that could significantly influence the pulmonary pathology. In all cases in Table 1 there were extensive lesions of the pulmonary vessels.

Most authors describe the severest lesions as being in the arterioles, the changes becoming less marked in the larger arteries. The lesion is generalized, in contrast to the predominance of change in the lower lobes in mitral stenosis.[49] Nearly every author describes intimal thickening as occurring most frequently in the form of fibroblastic proliferation (endarteritis obliterans).[50] This was particularly striking in our Case 1 (Figs. 3, 4, and 5). The sections in Cases 2 and 3 presented fibrous intimal thickening, but the process appeared much older with considerable hyaline change. Some authors describe few to many arteriolar thrombi, both old and recent. It is likely that such thrombi are formed *in situ* as a result of endothelial damage. The medial changes have been given more attention in recent literature. Some authors have noted little or no change in the arteriolar media.[51] Brenner described a rather uniform muscular hypertrophy. Gilmour and Evans,[28h] in an exhaustive study, described segments of hypertrophy and segments of abnormally thin media. The latter were covered by edematous granulation tissue. Arteriolonecrosis was not seen in any of the cases tabulated. The adventitial lesions have usually not been considered at length. In some cases, such as that of Brenner, the adventitia was thickened and contained foci of lymphocytes. Frequently, as in our cases, there was no significant change.

Changes in the muscular arteries usually consisted of fibrous intimal thickening, but narrowing of the lumens was not usually as severe as in the arterioles. The main

49. Parker, F., Jr., and Weiss, S.: Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573, 1936.

50. Barlaro.[18] Brill and Krygier.[20e] Footnote 28 *h* and *k*.

51. Brill and Krygier.[20e] Sokoloff and Stewart.[28g]

branches of the pulmonary artery contained atheromatous changes similar to those so frequently found in the aorta.

As emphasized by Brenner, minor variations in the histopathology of these lesions occur. In addition, Brenner noted that it was impossible to distinguish a case of primary arteriolosclerosis from one of secondary arteriolar lesions by the histologic changes of the arterioles. This has been entirely true in our experience. The literature contains many illustrations of secondary lesions which are identical to those described for the primary disease.[52]

Because the arteriolar lesion is not specific, it is important to note other changes in the lungs. Often these are more important diagnostically than the arteriolar lesions. Most authors have described few, if any, changes in the alveolar walls.[20c] Thickening of the walls of the capillaries may be present.[28g] In general, cases which have extensive thickening of alveolar walls and septa with either fibrous tissue or inflammatory cells have not been confirmed in other respects as cases of primary arteriolar disease. Also, the presence of hemosiderin-laden phagocytes in significant numbers in alveolar lumens would not be expected. Chronic bronchitis or bronchiectasis was not pronounced in any case. Emphysema was not present in significant degree.

Microscopic changes in the other organs of the body were usually few. Changes that were present could be readily explainable as either incidental or secondary to the pulmonary vascular lesions. In none of the cases in Table 1 were significant vascular lesions reported in organs other than the lungs.

SECONDARY PULMONARY ARTERIOLOSCLEROSIS

A discussion on the diagnosis of primary pulmonary arteriolosclerosis necessitates the inclusion of the various pathologic states which simulate it clinically and pathologically. It is these secondary vascular lesions that have attracted the attention of most writers on the subject of pulmonary vascular sclerosis. Since space precludes discussion of each of the numerous diseases associated with these lesions of the lesser circulation, their grouping in the following broad classification is presented.

I. Cardiac lesions
   - A. Congenital defects of the heart involving arteriovenous shunts
   - B. Valvular disease
   - C. Patent ductus arteriosus
   - D. Cardiac failure (left)

II. Lesions producing diminution of functional lung volume
   - A. Lesions of the pulmonary parenchyma
     1. Emphysema
     2. Neoplasia
     3. Inflammation (particularly chronic)
        - *a.* Viral, bacterial, and parasitic
        - *b.* Chemical (silica, etc.)

52. Killingsworth and Gibson,[26h] Leopold, S. S.: The Etiology of Pulmonary Arteriolosclerosis (Ayerza's Syndrome) with Report of an Illustrative Case, Am. J. M. Sc. **219**:152, 1950. Selzer, A., and Laqueur, G. L.: The Eisenmenger Complex and Its Relation to the Uncomplicated Defect of the Ventricular Septum: Review of 35 Autopsied Cases of Eisenmenger's Complex, Including 2 New Cases, A. M. A. Arch. Int. Med. **87**:218, 1951.

B. Extrapulmonary lesions

1. Deformities of bony thorax (kyphoscoliosis)
2. Pleural involvement (neoplasia, inflammation)
3. Mediastinal tumor

III. Vascular disease of lungs

A. Thrombosis and embolism

B. Raynaud's disease [53]

C. Scleroderma

D. Inflammation (syphilis, rheumatic fever)

IV. Metabolic diseases (xanthomatoses)

Of these, most are infrequently encountered. However, the incidence of pulmonary arteriolosclerosis in the presence of multiple pulmonary emboli or thrombi, emphysema, mitral stenosis, and certain congenital cardiovascular lesions is sufficiently high to be classed as not uncommon.

SUMMARY

Twenty-eight cases of primary pulmonary arteriolosclerosis collected from the literature are presented, and three additional cases are reported. A review of the clinical and pathologic findings is presented. The disease is manifested in its early phase by respiratory symptoms and terminally by the signs and symptoms of right-heart failure. The outstanding pathologic lesion is a severe fibrous intimal thickening of the pulmonary arterioles, as well as hypertrophy and dilatation of the right ventricle. The diagnosis may be suspected during life by detailed clinical evaluation but is established with reasonable certainty only by microscopic examination of a lung biopsy specimen. The disease is discussed with special reference to similar lesions of the pulmonary arterioles occurring during the course of other diseases. The causation and pathogenesis are not known. The role of primary or essential pulmonary arterial hypertension with resultant vascular hypoxia is discussed.

53. Linenthal, H.: Observations Concerning Pulmonary Fibrosis in Raynaud's Disease, New England J. Med. **227**:433, 1942.

OUTPATIENT TREATMENT OF CONGESTIVE HEART FAILURE WITH SODIUM-REMOVING EXCHANGE RESINS

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MOST OF the published reports on the use of cation-exchange resins in the treatment of congestive heart failure have been concerned primarily with hospitalized patients.[1] Since patients with congestive heart failure are treated largely on an ambulatory basis, it is even more important to evaluate the usefulness of these new therapeutic agents under conditions similar to those occurring in the average outpatient practice.[2] The present communication reports experiences with a group of such patients whose previous clinical courses and therapeutic responses to the usual cardiac regimens are particularly well documented.

MATERIALS AND METHODS

The 10 patients in this series were in congestive heart failure, previously not well controlled by digitalis, low-sodium diet, oxygen, and frequent use of mercurial diuretics. Six had rheumatic, two arteriosclerotic, one rheumatic and hypertensive, and one hypertensive heart disease. All had been followed in the hospital wards, in the clinic, or through the Home Care Program for one-half to six years prior to resin therapy. The pertinent observations were made through the Home Care Program, although administration of resins was started for two patients in the hospital. For six months to two years prior to resin therapy, the other eight had been carefully followed at home by physicians, visiting nurses, and social workers, as their needs indicated. Their characteristic therapeutic response was, therefore, well established.

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1. (*a*) Dock, W.: Sodium Depletion as a Therapeutic Procedure: The Value of Ion-Exchange Resins in Withdrawing Sodium from the Body, Tr. A. Am. Physicians **59**:282 (May) 1946. (*b*) Irwin, L.; Berger, E.; Rosenberg, B., and Jackenthal, R.: The Effect of a Cation Exchange Resin on Electrolyte Balance and Its Use in Edematous States, J. Clin. Invest. **28**(Pt. 2):1403 (Nov.) 1949. (*c*) McChesney, E. W.; Dock, W., and Tainter, M. L.: Ion Exchange Resins in Edema, Medicine **30**:183 (May) 1951. (*d*) Emerson, K., Jr.; Kahn, S. S.; Vester, J. W., and Nelson, K. D.: Oral Use of Cation-Exchange Resins in Treatment of Edema, A. M. A. Arch. Int. Med. **88**:605 (Nov.) 1951. (*e*) Danowski, T. S.; Greenman, L.; Mateer, F.; Peters, J. H.; Wiegand, F. A.; Mermelstein, H., and Clarke, C. E.: Carboxylic Cation Exchange Resin Studies in Animals and Humans, J. Clin. Invest. **29**:807 (June) 1950. (*f*) Martz, B. L.; Kohlstaedt, K. G., and Helmer, O. M.: Use of a Combination of Anion and Cation Exchange Resins in the Treatment of Edema and Ascites, Circulation **4**:524 (April) 1952.

2. Kleiber, E. E., and Pickar, G.: Treatment of Chronic Congestive Cardiac Failure with Ion Exchange Resins, Ann. Int. Med. **34**:407 (Feb.) 1951. Feinberg, A. W., and Rosenberg, B.: The Use of a Carboxylic Cation Exchange Resin in the Therapy of Congestive Heart Failure, Am. Heart J. **42**:698 (Nov.) 1951.

The preparation of a low-sodium diet, calculated to contain less than 0.5 gm. of sodium daily, was explained by hospital dietitians and visiting nurses. However, actual daily sodium intakes were probably 1.5 to 2.0 gm. Daily weights were recorded. Mimeographed instructions and precautions (Table) were distributed with the resin.

"Carboresin,"[3] a mixture containing 12% anion-exchange resin and 88% carboxylic-acid-type cation-exchange resins, two-thirds in the hydrogen cycle and one-third in the potassium cycle, was used throughout this study. The mixture was prescribed in tablespoon doses, each containing approximately 7 gm. From 21 to 70 gm. was given daily in divided doses one-half hour after each meal, so distributed that more was taken after the largest meal. The duration of therapy depended upon the response.

Chemical analyses of the serum, collected from the fasting patients before the beginning of resin therapy and subsequently at suitable intervals, were performed by the following methods: Sodium and potassium were assayed by means of a lithium internal standard flame photometer; chloride, by a modification of Sendroy's iodometric method,[4] and carbon dioxide content, by the Van Slyke manometric method.[5]

Instructions for Patients on Home Care Program Using Resins

1. Fruit juices:	It is extremely important that you take at least 2 full glasses of citrus fruit juice daily. Orange juice is recommended.
2. Vomiting:	Vomiting is a danger signal, and use of the resins should be discontinued. The Home Care Office should be informed immediately.
3. Constipation:	Constipation may be caused by the resin. This is usually mild and not dangerous. It can usually be overcome by enemas or mild laxatives, to be prescribed by your doctor.
4. Diarrhea:	Diarrhea is infrequently caused by the resin. If diarrhea occurs, notify the Home Care Office.
5. Marked weakness:	Marked weakness may be a danger signal, and the Home Care Office should be notified.
6. Blood tests.	Blood tests are necessary to determine your individual needs for the resin. These will be done at weekly or two-weekly intervals, as determined by your doctor.

RESULTS

The relevant findings before, during, and after resin therapy are illustrated in Charts 1 to 10. Although the pre-resin-therapy control periods were often of years' duration, much shorter control periods are presented in the charts for convenience.

PATIENT H. D. (Hospital No. 38892; Chart 1).—A 41-year-old woman with rheumatic and hypertensive heart disease, mitral insufficiency and stenosis, and auricular fibrillation had been in congestive failure for three years. Despite adequate digitalization, low-sodium diet, and frequent use of mercurials during the previous nine months on the Home Care Program, she was not well controlled.

Four months prior to the charted period a trial of 42 gm. of resin given daily in the hospital was terminated when severe anorexia developed. However, at home, when an initial daily dose of 21 gm. was slowly increased to 42 gm., resins were well tolerated and resulted in an 8-lb. (3.6-kg.) weight loss and relief of cardiac symptoms. Since then, although permitted an unrestricted diet, the patient has remained well controlled with only infrequent administration of mercurials.

3. "Carboresin" (sodium-removing resin) is a mixture of two forms of the carboxylic acid cation exchanger, amberlite® XE-64, a cross linked acrylic acid polymer, and an anion exchanger, alkylene polyamine resin, XE-58. The resin was supplied through the courtesy of Dr. Kenneth G. Kohlstaedt, of Eli Lilly & Co.

4. Van Slyke, D. D., and Hiller, A.: Application of Sendroy's Iodometric Chloride Titration to Protein-Containing Fluids, J. Biol. Chem. **167**:107 (Jan.) 1947.

5. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in the Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523 (Sept.) 1924.

For the past seven months she has been taking resin daily without gastrointestinal symptoms or significant change in serum electrolyte concentrations.

PATIENT J. C. (Hospital No. 52087; Chart 2).—A 48-year-old woman with rheumatic heart disease, mitral insufficiency and stenosis, and auricular fibrillation was in congestive failure for three years. During 23 months on the Home Care Program she was poorly controlled by digitalization, low-sodium diet, and frequent use of mercurials.

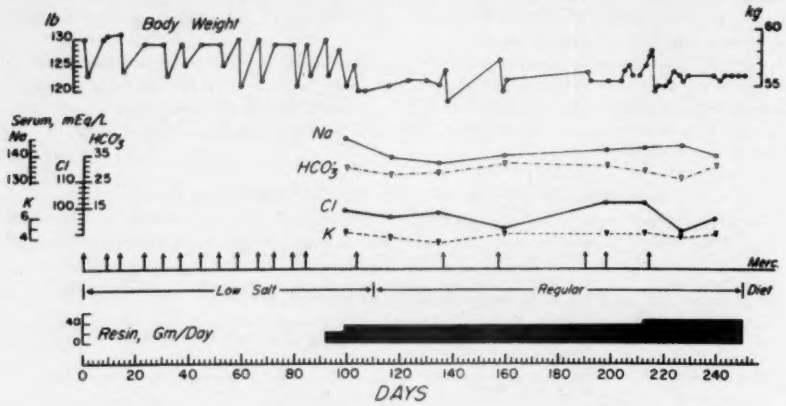

Chart 1 (Patient H. D.).—Previous intolerance for resin overcome by gradual increase of dose in a woman aged 41. Note infrequent need for mercurials even with regular diet.

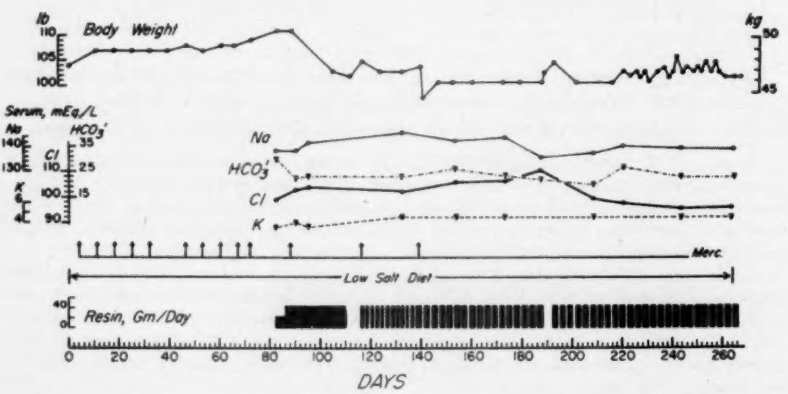

Chart 2 (Patient J. C.).—Intermittent resin therapy to prevent gastrointestinal irritation in a woman aged 48. Good control of congestive failure without mercurials. Transient mild acidosis.

On administration of 42 gm. of resin daily she lost 9 lb. (4.1 kg.) without use of mercurials and within two weeks was free of edema and dyspnea. After discontinuing the resin therapy for one week because of anorexia and constipation, she resumed the same daily resin dosage but omitted the dose at first on alternate days and later on every third day. Again, a good therapeutic effect was obtained, this time without gastrointestinal symptoms.

She has been receiving resins for six months and has not required administration of a mercurial for five months. On two occasions, discontinuance of resin therapy for a week resulted in a 4-lb. (1.8-kg.) weight gain. She has had some mild constipation which is relieved by treatment with methylcellulose, occasional enemas, and increased water intake. Electrolyte determinations revealed a temporary mild acidosis with normal serum sodium and potassium concentrations.

PATIENT M. W. (Hospital No. 48557; Chart 3).—A 38-year-old woman with rheumatic heart disease, mitral insufficiency and stenosis, aortic insufficiency, tricuspid insufficiency, and auricular fibrillation was in congestive failure for six years. During two years on the Home Care Program, she did not respond well to the usual cardiac management, including daily intravenous administration of mercurials.

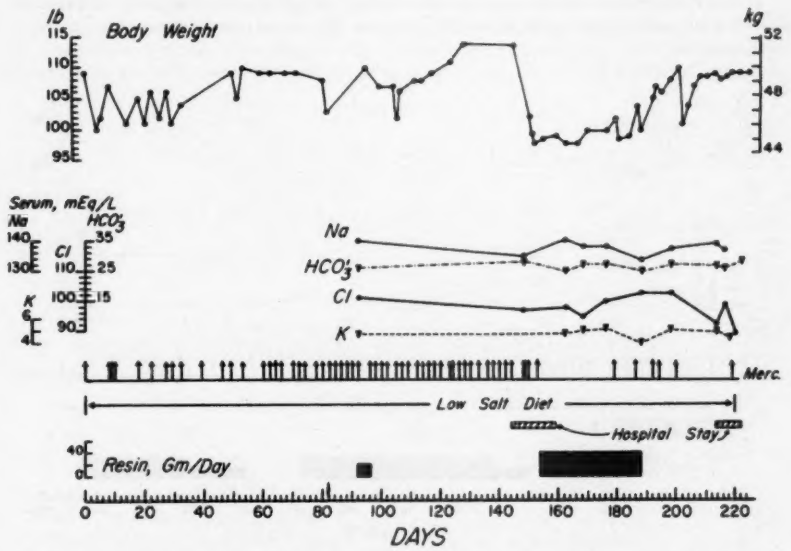

Chart 3 (Patient M. W.).—Good response of intractable heart failure to resin therapy in a woman aged 38. Resin therapy discontinued after one month. Note rapid return to control status after discontinuance of resins because of gastrointestinal intolerance.

An initial trial of 21 gm. of resin daily was terminated after four days because of nausea and diarrhea. Subsequently, she was hospitalized, and, with bed rest plus the more rigidly controlled hospital low-sodium diet, she lost 16 lb. (7.3 kg.) with marked symptomatic improvement. Just prior to discharge from the hospital, treatment with 42 gm. of resin daily was started, supplemented with potassium salts. This regimen was continued at home, and without use of mercurials she did not gain weight for one month. Although she continued to have epigastric distress and constipation, which was only partly relieved by mild laxatives, enema, and increased fluid intake, she was otherwise so improved that she refused to discontinue resin therapy until gastrointestinal symptoms became severe. Soon thereafter, despite mercurial diuretics, she quickly reaccumulated edema fluid, became increasingly dyspneic, and was rehospitalized. To date, she has not been given resin and has not responded well to other therapy.

While she received resin, a mild, asymptomatic acidosis developed, with an insignificant fall in serum sodium concentration.

PATIENT F. B. (Hospital No. 46802, Chart 4).—A 52-year-old woman with rheumatic heart disease, mitral insufficiency and stenosis, and regular sinus rhythm with paroxysmal auricular tachycardia was in congestive failure for 12 years. During 28 months on the Home Care Program she had not been well controlled by digitalization, low-sodium diet, and frequent administration of mercurials.

Within two months of therapy with 42 gm. of resin daily, edema and dyspnea diminished without use of mercurials. Later, with administration of 21 gm. daily, biweekly injections of mercurials were required to prevent reaccumulation of edema fluid.

Except for epigastric distress, which subsided without specific therapy, and later mild constipation, which was relieved by enemas and increased fluid intake, she had no serious gastrointestinal complaints. With symptomatic improvement, her appetite increased remarkably and her weight was maintained despite mobilization of edema fluid.

With the larger doses of the resin she exhibited a mild, asymptomatic acidosis, with reduced serum carbon doxide content, elevated serum chlorides, and normal serum sodium and potassium concentrations.

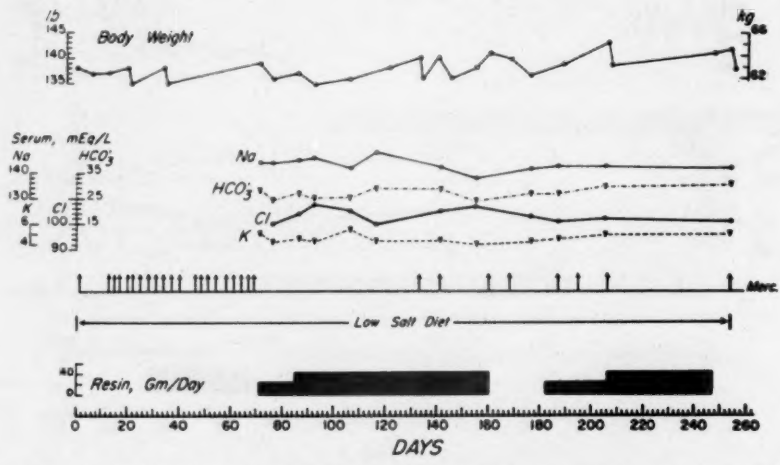

Chart 4 (Patient F. B.).—Successful substitution of resins for frequent use of mercurials in a woman aged 52. Increased food intake maintained the body weight despite loss of edema. Note prompt changes of weight upon withdrawal or resumption of resin therapy.

PATIENT C. F. (Hospital No. 48957; Chart 5).—A 38-year-old woman with rheumatic heart disease, mitral insufficiency and stenosis, and auricular fibrillation was in congestive failure for three years. During the previous 25 months on the Home Care Program she was not well controlled by adequate digitalization, low-sodium diet, and frequent administration of mercurials. After pretreatment with ammonium chloride, mercurials promoted good diureses which, however, were associated with vomiting.

Resin administration had to be discontinued after a few days on two initial attempts because of nausea, diarrhea, and constipation. Finally, after repeated reassurance that the gastrointestinal symptoms would be mild and would subside after a few weeks of therapy, a third attempt was successful, and she tolerated 42 gm. daily for six weeks with only mild epigastric cramps and constipation which responded to enemas and administration of magnesia magma (milk of magnesia). For one month use of mercurials was required less frequently and produced the same enhanced diureses observed after pretreatment with ammonium chloride. Subsequently, however, she gradually reaccumulated edema fluid, and her mercurial requirements increased. A larger resin dose was not tolerated because of increased constipation and anorexia.

While she received resins, moderate acidosis developed which was corrected by mercurials. Serum sodium and potassium concentrations were not significantly altered.

PATIENT M. F. (Hospital No. 51029; Chart 6).—A 60-year-old woman with rheumatic heart disease, mitral insufficiency and stenosis, aortic insufficiency and stenosis, and auricular fibrillation had been in severe congestive failure for three years. Although in the arteriosclerotic age group, she exhibited no clinical evidence of organic renal disease. During the previous 12 months on the Home Care Program, massive anasarca had slowly developed despite adequate digitalization, low-sodium diet, use of oxygen, and frequent administration of mercurials. When she was hospitalized, her serum sodium, chloride, and potassium concentrations were subnormal.

On the hospital low-sodium diet, intermittent resin therapy, without use of mercurials, resulted in a 33-lb. (15-kg.) weight loss, while serum electrolyte studies revealed a rise in chloride and a fall in sodium and potassium which was corrected by administration of potassium supplements. With each course of resin therapy there were disturbing fecal impactions.

At home the administration of 42 gm. of resin daily with supplemental potassium salts was continued for one month. After three weeks of good therapeutic response, she exhibited severe weakness, anorexia, and vomiting, and her serum sodium and chloride fell to 106 mEq. per liter

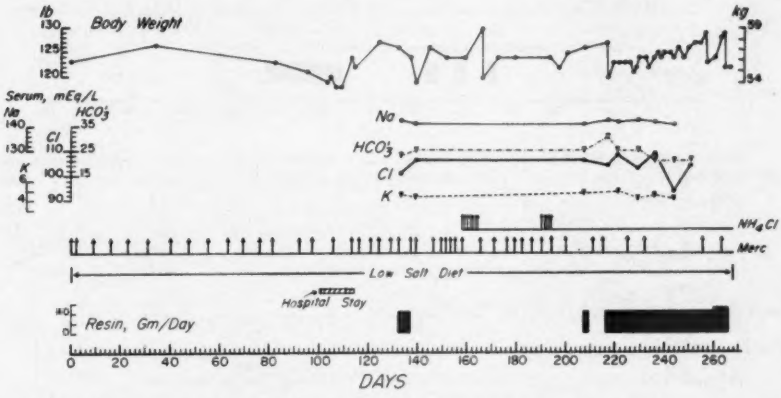

Chart 5 (Patient C. F.).—Inability to achieve therapeutic doses of resins because of gastrointestinal symptoms in a woman aged 38. Note transient mild acidosis.

(244 mg. per 100cc.) and 82 mEq. per liter (301 mg. per 100 cc.), respectively. This hyponatremia was successfully treated in the hospital, but, after her discharge, resin therapy was not resumed. Despite administration of ammonium chloride and frequent use of mercurials, without resin therapy, she again exhibited anasarca and hyponatremia and was readmitted to the hospital after gaining 24 lb. (10.9 kg.).

PATIENT A. D. (Hospital No. 51007; Chart 7).—A 49-year-old man with rheumatic heart disease, mitral insufficiency and stenosis, and regular sinus rhythm was hospitalized with a history of increasing congestive failure following subacute bacterial endocarditis. He had not previously been followed on the Home Care Program.

Despite rest, digitalization, and the hospital low-sodium diet, he was not relieved of cardiac symptoms. With resin therapy, his weight fell from 104 to 90 lb. (from 47.2 to 40.8 kg.), his dyspnea and orthopnea subsided, and only mild constipation, asymptomatic persistent acidosis, and slightly decreased serum sodium concentrations were noted. Adding 3 gm. of sodium chloride to his daily diet resulted in neither weight gain nor recurrence of symptoms, and his serum electrolyte concentrations approached normal.

After discharge from the hospital, he received no resin. After a two-week vacation during which he did not remain on the low-sodium diet, he was transferred to the Home Care Program. At this time, because of increased congestive failure, he was given two mercurial injections

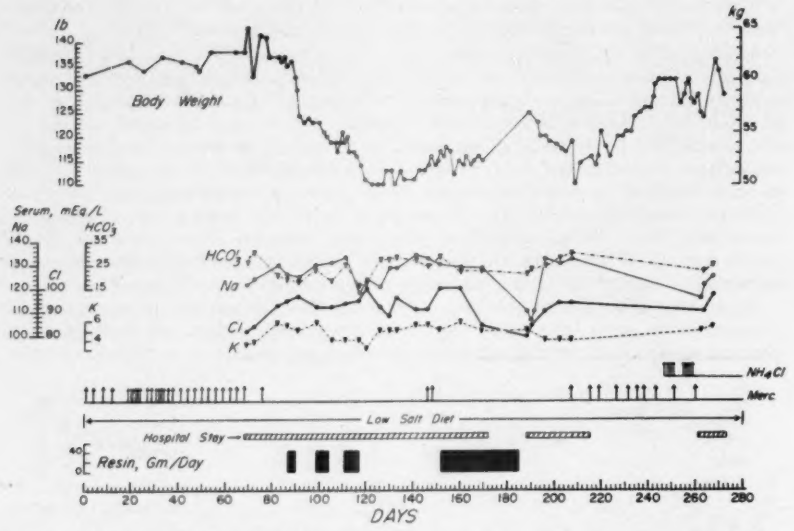

Chart 6 (Patient M. F.).—Relief of anasarca in a woman aged 60 without use of mercurials by resin therapy in the hospital. Note recurring hyponatremia with and without resins at home.

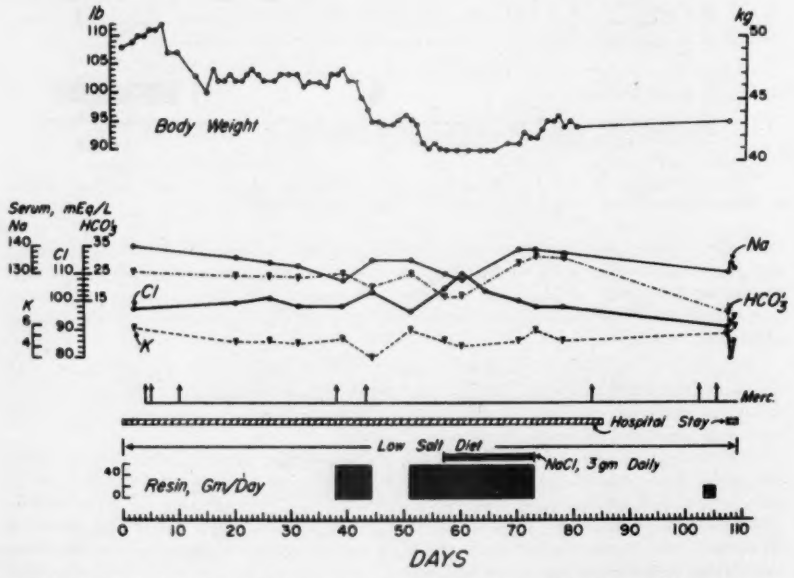

Chart 7 (Patient A. D.).—Good control of congestive failure in hospital on resins, even with added salt, in a man aged 49. Note mild acidosis and fall in serum sodium. After discharge, heart failure increased while patient was not under continued medical supervision and was not receiving resins. Death in shock and acidosis related to severe hepatic congestion.

within a week and, without consulting his physician, took small but undetermined amounts of resin for two days. A few days later he complained of abdominal pain, weakness, nausea, and vomiting. He was promptly rehospitalized but was in shock and severe acidosis, with a serum carbon dioxide concentration of 6.6 mEq. per liter (14.7 vol. %), but with serum chloride and sodium concentrations of 90 mEq. per liter (330 mg. per 100 cc.) and 131 mEq. per liter (301 mg. per 100 cc.), respectively. Despite vigorous therapy, he died the following day. Postmortem examination confirmed the cardiac diagnoses and the presence of severe visceral chronic passive congestion. There was no organic renal pathology.

PATIENT H. F. (Hospital No. 49408; Chart 8).—A 63-year-old man with arteriosclerotic heart disease was in congestive failure for three years. After four weeks of hospitalization, he was unimproved despite digitalization, sodium restriction, and frequent, ineffective use of mercurials. During the following month of hospitalization, while taking 56 to 70 gm. of resin daily, he lost 10 lb. (4.5 kg.) and improved markedly while receiving only one mercurial injection.

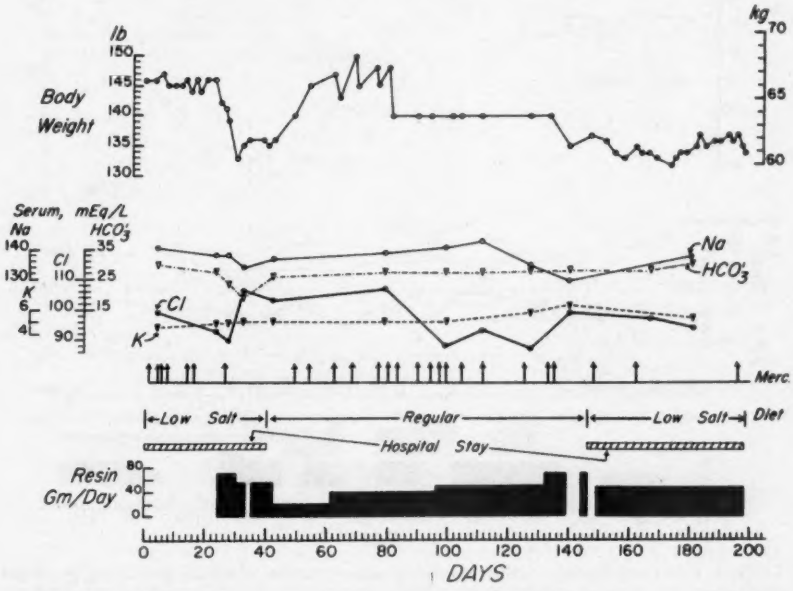

Chart 8 (Patient H. F.).—Good control of congestive failure with resins in a man aged 63 on regular diet. Early transient acidosis; later, fall in serum sodium, corrected by omitting resins for six days.

After discharge, the daily resin dose was reduced to 21 gm., and he was given mercurials weekly in the clinic. Because he ate in restaurants, he could not remain on a low-sodium diet and gained 18 lb. (8.2 kg.), reaccumulated edema fluid, and became dyspneic. Then he was placed on the Home Care Program, the dose of resin was increased to 42 gm. daily, and the weekly administration of mercurials was continued. Within two weeks, despite the unrestricted diet, he lost 10 lb. (4.5 kg.) and was relieved of dyspnea. Although his serum sodium concentration fell from 141 to 136 mEq. per liter, resin dosage was increased to 70 gm. daily for six days, and he lost an additional 5 lb. (2.3 kg.). However, because of nausea, vomiting, and a further decrease in his serum sodium concentration to 130 mEq. per liter, the resin therapy was stopped. A week later, after gastrointestinal symptoms had subsided and serum sodium concentration had returned to normal, smaller doses of the resin were given without incident, but administration of mercurials was needed more frequently.

Subsequently, he was rehospitalized during an attack of angina. With a low-sodium diet, 49 gm. of resin daily, and three injections of mercurials in two months, he lost 8 lb. (3.6 kg.) more and was again edema free. During this period he had only mild, asymptomatic acidosis and mild constipation, which was relieved by enemas.

PATIENT H. S. (Hospital No. 47192; Chart 9).—A 72-year-old man with bronchial asthma and arteriosclerotic heart disease was in severe congestive failure for seven years. On the Home Care Program he rejected salt restriction; despite adequate digitalization and frequent administration of mercurials for 30 months, he had marked dyspnea and edema and was confined to bed.

A regimen of 21 gm. of resin daily was terminated after 17 days because he lost no edema fluid, was symptomatically unchanged, and had anorexia and constipation. Later, however, when 42 gm. of resin was given daily, there were marked symptomatic improvement and an 18-lb.

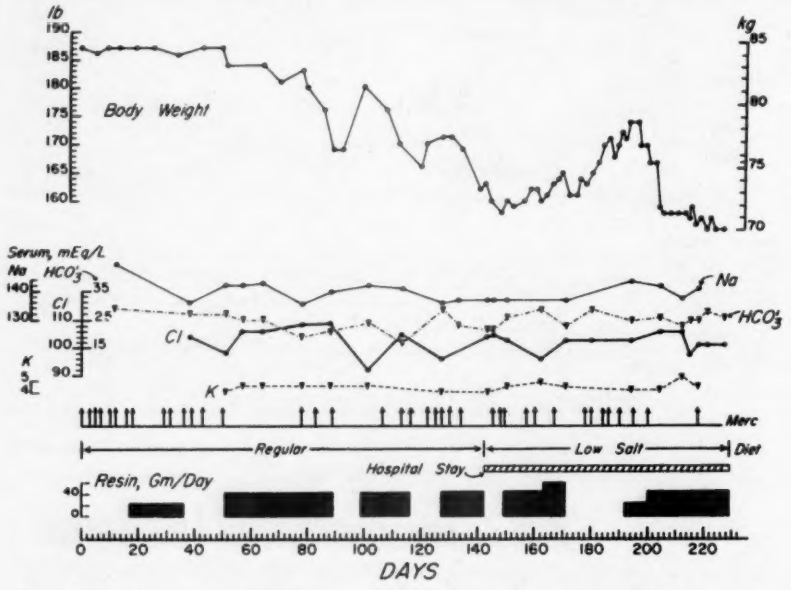

Chart 9 (Patient H. S.).—Relief of congestive heart failure in a man aged 72 by prolonged intermittent use of resins without severe acidosis.

(8.2-kg.) weight loss in 39 days with only infrequent use of mercurials. He felt so much better that he continued taking the resin despite constipation and abdominal cramps. However, serum carbon dioxide content fell gradually to 17 mEq. per liter (37.7 vol. %) and serum chloride concentration rose to 109 mEq. per liter (382 mg. per 100 cc.). Therefore, resin therapy was discontinued, and he rapidly reaccumulated edema fluid, gaining 11 lb. (5 kg.) in 10 days. The blood urea nitrogen remained normal, and the urine had a trace of albumin.

Subsequently, he was given resin intermittently for two- to three-week periods. Each course was terminated whenever he became acidotic. With this management, he maintained his additional 15-lb. (6.8-kg.) weight loss, despite the regular diet and the less frequent use of mercurials.

Later, when rehospitalized because of a severe asthmatic attack, he had no further weight loss with resin therapy despite the low-sodium diet. When resin administration was stopped for 23 days, he reaccumulated edema fluid and gained 12 lb. (5.4 kg.). When resins were again administered, he improved markedly and lost 19 lb. (8.6 kg.) in 10 days. During the next seven weeks with resin therapy he showed only a mild acidosis and rarely required mercurials. Moderate constipation was somewhat relieved by use of mild laxatives and occasional enemas.

PATIENT A. W. (Hospital No. 52540; Chart 10).—A 49-year-old man with hypertensive heart disease was in congestive failure for five years. During the previous six months on the Home Care Program, he was poorly controlled despite digitalization, use of oxygen and ammonium chloride, and frequent administration of mercurials. He was uncooperative and difficult to manage and refused to follow instructions, to take prescribed medications, or to adhere to a low-sodium diet; on one occasion, against advice, he took ammonium chloride while taking the resin. He did not respond to 63 gm. of resin daily and refused to increase the dosage because of constipation.

During hospitalization, his congestive heart failure was well controlled without resins by a low-sodium diet and frequent administration of mercurials followed by aminophylline.

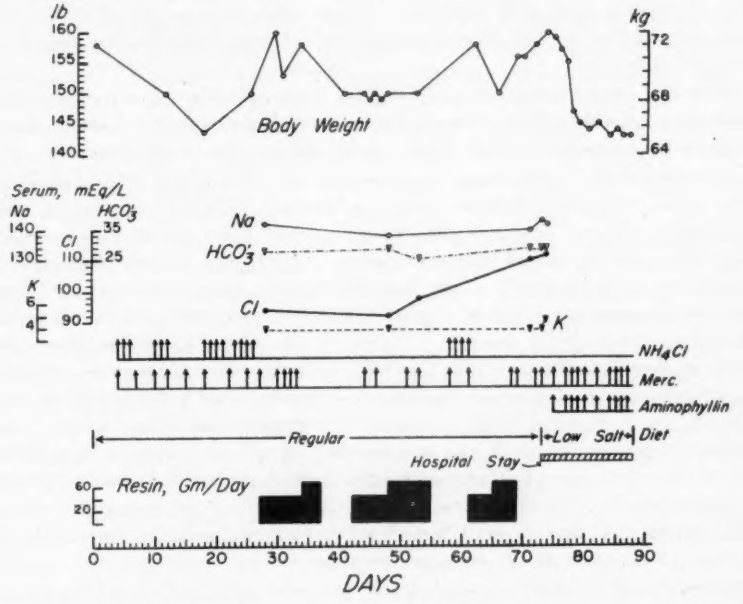

Chart 10 (Patient A. W.).—Poor control of heart failure at home in a man aged 49 on regular diet and resin therapy. Good response in hospital to low-sodium diet, frequent use of mercurials, and administration of aminophylline.

COMMENT

When investigating the effectiveness of a new drug, obtaining adequate control observations is always a major problem. In the present study this difficulty has been largely overcome because of the well-documented previous clinical and therapeutic courses of the 10 patients, 8 of whom were followed closely on the Home Care Program for months to years. The other two patients had been carefully observed in the hospital and subsequently followed on the Home Care Program. All were in chronic congestive heart failure and had responded poorly to the usual cardiac regimens. Therefore, under conditions closely simulating home or office practice, their response to the ion-exchange resins could be accurately evaluated.

The results in this series demonstrate the general usefulness and advantages of the ion-exchange resins in the treatment of congestive heart failure. In two

patients, however, a good therapeutic effect could not be achieved with resins. One, A. W. (Chart 10), was difficult to manage at home but under hospital conditions was better controlled by other measures. The other, C. F. (Chart 5), temporarily required less frequent use of mercurials while taking the resin but had no other significant change in her clinical course. During resin therapy in the eight remaining patients, including M. W. (Chart 3) for whom resin therapy was discontinued because of gastrointestinal irritation, there was not only reduced need for mercurials but also more effective control of congestive heart failure than could be achieved by any other means. Patient A. D. (Chart 7), who remained symptom free with resin therapy in the hospital even on an increased sodium intake, had a rapid downhill course after discharge without resin therapy. It is difficult to determine whether stricter dietary control and adequate resin therapy may have prevented this.

Although therapeutically effective, sodium-removing resins may produce certain unfavorable effects—gastrointestinal disturbances, hyperchloremic acidosis, hyponatremia, and hypopotassemia—which should be familiar to the physician.

Gastrointestinal Symptoms.—Not every patient can tolerate resins well,[1c] and some gastrointestinal symptoms, such as anorexia, nausea, constipation, and occasionally diarrhea, generally develop. However, these symptoms are usually mild, often may be allayed by reassuring the patient, may subside spontaneously if resin therapy is continued, or can easily be treated. The severer signs of gastrointestinal irritation can often be avoided either by starting with small amounts and gradually increasing the dose (cf. Patient H. D., Chart 1) or by intermittent administration (cf. Patient J. C., Chart 2). Furthermore, although "carboresin" is generally given as a simple suspension in water, some patients find it more palatable in fruit juice, milk, or cereal. Constipation, the most frequent and annoying symptom, generally can be controlled by occasional enemas, administration of methylcellulose or other mild laxatives, and increased fluid intake. Unfortunately, there are some patients in whom therapeutic doses cannot be reached (cf. Patients C. F. and A. W., Charts 5 and 10) or continued (cf. Patient M. W., Chart 3) because of severe gastrointestinal distress.

Acidosis.—Since the therapeutic effect of cation-exchange resins is promotion of the loss of sodium from the gastrointestinal tract, this leads to relative excess of chloride and an acidosis similar to that following ammonium chloride administration.[6] If renal function is adequate, increased urinary ammonia and titratable acid production and chloride excretion will compensate for the acidosis. However, if renal function is impaired and acid and ammonia production and chloride excretion are reduced, severe acidosis may develop.[1b]

As edema fluid was mobilized, all patients demonstrated a mild acidosis, but with continued use of the resin this generally was compensated. Although Patient H. S. (Chart 9) had no demonstrable renal disease, he had generalized arteriosclerotic vascular disease and exhibited moderately severe acidosis while receiving

6. Greenman, L.; Peters, J. H.; Mateer, F. M.; Wiegand, F. A.; Williams, D.; Tarail, R.; Rhodes, G., and Danowski, T. S.: Biochemical Changes Accompanying the Ingestion of a Carboxylic Cation Exchanger in the Hydrogen, Ammonium, Sodium, Potassium, or Calcium Form, J. Clin. Invest. **30**:995 (Sept.) 1951.

the resin. Intermittent use of the resin, guided by serum electrolyte determinations, permitted advantage to be taken of the therapeutic effect without producing persistent, symptomatic acidosis.

Patient A. D. (Chart 7) had no renal pathology and had been taking only small doses of the resin for a few days, when he was hospitalized in severe shock and acidosis. In the light of previous metabolic studies on this patient, it is difficult to implicate the resin as an etiological factor, since his serum sodium concentration was not much reduced and the fall in his carbon dioxide level was not accompanied with the characteristic equivalent increase in serum chlorides.

When the serum carbon dioxide is above 20 mEq. per liter (44 vol.%), resin therapy need not be discontinued. In fact, such mild acidosis serves to potentiate the diuretic action of mercurials, if required.[1g] However, persistent nausea or vomiting, or severe acidosis with the carbon dioxide below 20 mEq. per liter, is an absolute contraindication to the continued use of the resin. Stopping the resin therapy and administering mercurials, which will promote chloride excretion, generally will lead to prompt recovery from acidosis.[7] By including some resin in the potassium cycle, as in "carboresin," additional cation is furnished which may help prevent acidosis.[1f]

Hyponatremia.—Although sodium depletion is another potential hazard of sodium-removing resin therapy, in 8 of our 10 patients the serum sodium concentration did not significantly change. However, after one month of resin therapy, Patient M. F. (Chart 6) was hospitalized with symptomatic hyponatremia. The resin probably contributed to this episode, but she previously and subsequently showed hyponatremia with mercurial injections and salt restriction without resin therapy. In the case of H. F. (Chart 8) one course of resin therapy was discontinued after a day of nausea and vomiting when it was noted that his serum sodium concentration had fallen 13 mEq. per liter in the preceding three weeks. Previous and subsequent courses were without incident.

The rare case of hyponatremia may be prevented by careful clinical observation and periodic determinations of serum electrolytes. It is more likely to occur after the patient on a salt-poor diet has become edema free. Consequently, at this time, the dose of resin should be reduced to the minimum effective quantity. When sodium determinations are not readily available, serum sodium concentrations may be estimated as the sum of the serum carbon dioxide and chloride concentrations + 10, all in milliequivalents per liter.[8] With renal disease or severe congestive heart failure, however, the accumulation of other organic or inorganic acids may make this calculation invalid. The usual clinical signs—nausea, vomiting, weakness, apathy, and other mental changes—when present, may warn the physician of impending or actual hyponatremia. Since these symptoms are not specific, it may be dangerous to omit serum electrolyte determinations in patients receiving resin therapy.

7. (*a*) Martz and others.[1f] (*b*) Weston, R. E.; Borun, E. R.; Grossman, J.; Guerin, H. A.; Ullmann, T. D.; Wolfman, M., and Leiter, L.: Metabolic Studies on Edematous Patients Treated with Ion Exchange Resins, to be published.

8. Hald, P. M.; Heinsen, A. J., and Peters, J. P.: The Estimation of Serum Sodium from Bicarbonate Plus Chloride, J. Clin. Invest. **36**:983 (Sept.) 1947.

Hypopotassemia.—Because the cation-exchange resin in the hydrogen cycle also removes potassium from the gastrointestinal tract, a mixture containing resin in the potassium cycle is given to prevent potassium depletion.[1c, f] As additional prophylaxis against negative potassium balance, all our patients were instructed to drink at least 2 glasses of orange juice daily, which supplied about 20 mEq. of potassium.[9] None showed evidence of potassium depletion. The administration of supplemental potassium salts (cf. Patients M. W. and M. F., Charts 3 and 6) is unnecessary when patients are eating well. Moreover, the fruit juices are more palatable and economical. It should be emphasized that resin therapy should be discontinued in the presence of vomiting or severe diarrhea, conditions which may produce considerable losses of potassium. When chemical data are unavailable, electrocardiographic evidence of hypopotassemia [10] or increased sensitivity to digitalis [11] may be used as an index of negative potassium balance. In this study, neither was encountered.

SUMMARY AND CONCLUSIONS

With adequate clinical and laboratory safeguards, sodium-removing resins are effective in the treatment of congestive heart failure. In eight patients, edema previously resistant to other forms of therapy was reduced, while the need for mercurial drugs was diminished or eliminated. Dyspnea and other symptoms of congestive heart failure were markedly alleviated, enabling the patients to live a more normal and active life. Two of these patients became able to tolerate unrestricted diets. The therapeutic effects were so comforting that some patients refused to discontinue taking the resin despite moderate gastrointestinal irritation.

Gastrointestinal symptoms are common but can usually be controlled. However, because of the occasional severity of such symptoms, some patients may be unable to take resin in therapeutic doses.

Serum electrolyte determinations before and during ion-exchange-resin therapy are extremely important for the proper management of the cardiac patient. Dangerous complications may be avoided by following the serum carbon dioxide and chloride levels, which will give an estimate of the serum sodium concentration, as well as the degree of acidosis. The frequency of these determinations should depend upon the patient's response to the resin. When renal pathology is suspected, or in persons of the old age groups, more frequent serum electrolyte analyses should be performed. For the purposes of this study, serum electrolyte concentrations were determined weekly at the onset of resin therapy to establish the pattern of response.

In the absence of laboratory facilities, extremely careful clinical supervision is essential. Most cardiac patients treated with the ion-exchange resin by the average physician probably will be in less severe congestive heart failure and under less

9. Bills, C. E.; McDonald, F. G.; Niederman, W., and Schwartz, M. C.: Sodium and Potassium in Foods and Waters, J. Am. Dietetic A. **25**:304 (April) 1949.

10. Finch, C. A.; Sawyer, C. G., and Flynn, J. M.: Clinical Syndrome of Potassium Intoxication, Am. J. Med. **1**:337, (Oct.) 1946.

11. Lown, B.; Salzberg, H.; Enselberg, C. D., and Weston, R. E.: Interrelation Between Potassium Metabolism and Digitalis Toxicity in Heart Failure, Proc. Soc. Exper. Biol. & Med. **76**:797 (May) 1951.

rigid sodium restriction than were the patients in this study. In such circumstances, electrolyte abnormalities are less likely to occur, but still better management is possible with chemical control.

It should be emphasized that there can be no routine treatment with ion-exchange resin. The dose, schedule, and duration of therapy, like the frequency of electrolyte determinations, must depend upon the clinical condition and response of the individual patient.

The present study demonstrates the usefulness of ion-exchange resins for outpatient treatment of congestive heart failure. The therapeutic effects achieved will depend upon careful evaluation and care of the patient by the physician. Like insulin, digitalis, mercurials, and other potent drugs, resins must be administered with full understanding of potentially harmful effects. Properly used, sodium-removing resins provide an effective method for controlling edema, even in patients resistant to other therapy.

Dr. I. Rossman assisted in the clinical care of the patients. Dr. L. Leiter made helpful suggestions. Mr. George Ross performed the laboratory analyses.

COMPLICATIONS IN THE USE OF ESOPHAGEAL COMPRESSION BALLOONS (SENGSTAKEN TUBE)

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LESTER BAKER, M.D.
AND
LYLE A. BAKER, M.D.
HINES, ILL.

THE USE of an esophageal compression tube for treatment of bleeding esophageal varices was described in 1948 by Tocantins [1] and in 1930 by Westphal (cited by Kaplan [2]). Since this time the successful use of esophageal tamponade has been repeatedly reported, and tube modifications have been described.[3]

Despite numerous and excellent reports on the successful use of these tubes as temporary emergency treatment for bleeding esophageal varices,[4] few if any complications from the use of these tubes have been reported. It is the purpose of this report to describe the complications we have encountered and to suggest methods to avoid these complications.

The Sengstaken tube has been employed at Hines Veterans Administration Hospital both with and without traction. Traction as recommended by Sengstaken and Blakemore [3b] has been employed, as well as a local modification consisting of a long elastic fastened to the tube at the nares and to an adhesive strap about the chest. This traction has been used when bleeding continues without traction.

From the Medical Services, Veterans Administration Hospital and Northwestern University Medical School.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Tocantins, L. M.: The Hemorrhagic Tendency in Congestive Splenomegaly (Banti's Syndrome), J. A. M. A. **136**:616-621 (Feb. 28) 1948.

2. Kaplan, B.: Esophageal Varices, M. Rec. **154**:176-180 (Sept. 3) 1941.

3. (*a*) Patton, T. B., and Johnston, C. G.: A Method for Control of Bleeding from Esophageal Varices, Arch. Surg. **59**:502-506 (Sept.) 1949. (*b*) Sengstaken, R. W., and Blakemore, A. H.: Balloon Tamponage for Control of Hemorrhage from Esophageal Varices, Ann. Surg. **131**:781-784 (May) 1950.

4. Kenamore, B., and Elliot, G.: The Control of Esophageal Hemorrhage by Pneumatic Tamponage and Thrombin, Gastroenterology **13**:73-76 (July) 1949. Barnett, C. B., and Cohen, S.: The Management of Massive Esophageal Hemorrhage with Tamponage and Thrombin, ibid. **13**:144-152 (Aug.) 1949. Requarth, W.: Diagnosis and Non-Surgical Treatment of Gastroesophageal Hemorrhage, S. Clin. North America **31**:201-211 (Feb.) 1951. Rowntree, L. G.; Zimmerman, E. F.; Todd, M. H., and Ajac, J.: Intraesophageal Venous Tamponage, J. A. M. A. **135**:630-631 (Nov. 8) 1947.

It is not the purpose of this paper to discuss the indications and contraindications for esophageal compressive treatment. Reference is made to previously cited reviews of this subject.

REPORT OF CASES

Approximately 60 patients have been treated with esophageal compression in the past 18 months at the Veterans Administration Hospital, Hines, Ill.; all but a few were treated for proved or suspected bleeding esophageal varices, the indicated use for such therapy. Five patients have suffered complications from the use of the tube, and one of these patients died. It is felt that the complication incident to the use of the tube contributed to this patient's death.

CASE 1.—A 34-year-old white man, with Laennec's cirrhosis and demonstrated (previous esophagoscopy) bleeding esophageal varices, was treated successfully upon previous hemorrhage with insertion of a Sengstaken tube,[3b] but the liver functions were too poor to accomplish

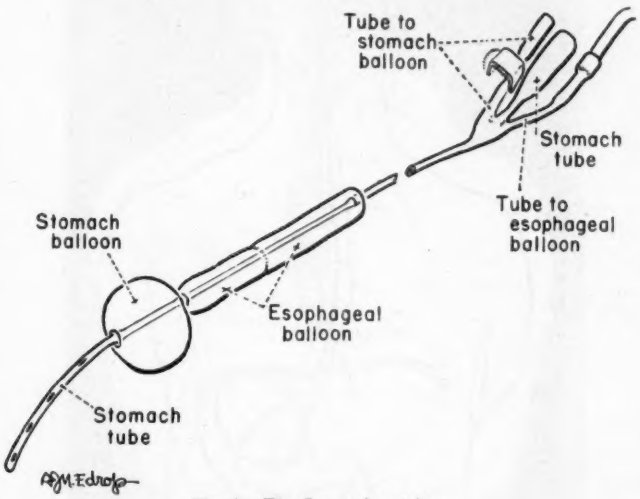

Fig. 1.—The Sengstaken tube.

splenorenal anastomosis. He was admitted to the hospital in shock with massive gastrointestinal hemorrhage. A Sengstaken tube was inserted and properly inflated, with traction applied by means of a large elastic band stretching from the tube at the nares to an adhesive band applied to the chest, thus maintaining constant traction of undetermined vigor. Within five minutes after insertion the tube had been regurgitated or pulled so that the inflated balloon was caught in the posterior pharyngeal cavity. The resident physician immediately deflated the tube and reinserted it with continued traction but no slippage. Two days later it was noted by an attendant that the patient's condition had suddenly become critical, and the physician was called. Upon arrival minutes later, the physician found the patient cyanotic with marked stridor. The patient's hand was to his mouth in an attempt to pull the tube out. The patient gave a few convulsive twitches and died despite resuscitation attempts. The esophageal balloon of the tube was found obstructing the posterior pharynx. Autopsy revealed esophageal varices with evidence of fresh bleeding and changes compatible with asphyxia.

CASE 2.—A 33-year-old white man had bleeding esophageal varices due to Laennec's cirrhosis. The tube slipped as in Case 1, with lodgment of the balloon in the posterior pharynx. The patient became cyanotic and was saved by quick action of attendant personnel, who transected the entire tube with scissors, thus allowing air to escape from the gastric bulb and esophageal

balloon. The tube was then quickly and easily removed. Insertion of another tube without traction stopped the bleeding.

CASE 3.—A 55-year-old man had repeated gastrointestinal hemorrhage both preceding and following gastric resection, presumably due to peptic ulceration. Peptic ulcer of the esophagus was visualized by esophagoscopy in 1949. The patient was admitted to the hospital in December, 1951, after massive hematemesis. A Sengstaken tube was inserted apparently in an attempt to control bleeding from an ulcer of the esophagus. No traction was applied to the tube. Ten minutes after the passage of the tube the patient suddenly became cyanotic. Rapid appraisal revealed that, despite lack of traction, the tube had been regurgitated and the inflated balloon was lodged in the posterior pharynx, obstructing breathing. Transection of the tube with scissors relieved the obstruction, and the tube was then easily removed. Autopsy following

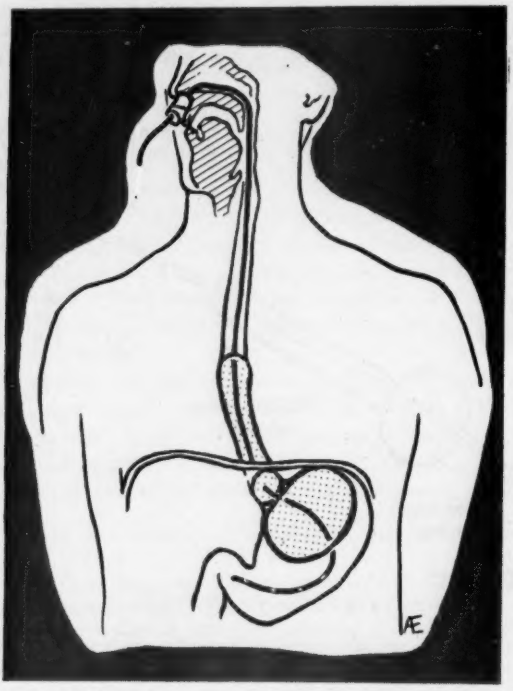

Fig. 2.—Correct placement of esophageal compression balloon.

death from continued hemorrhage revealed a hiatus hernia, congenitally short esophagus, and superficial erosions of the esophagus. Whether these were due to pressure of the tube or to peptic erosion could not be determined.

CASE 4.—A 33-year-old man had bleeding esophageal varices, secondary to Laennec's cirrhosis. The tube placed without traction was effective in controlling hemorrhage. An attempt at removal after 62 hours was difficult owing to failure of the lumen of tube to the balloon to open after prolonged clamping and resultant "cementing" of rubber at the clamp site. Traction on the tube by the resident physician resulted in lodging of the inflated balloon in the posterior pharynx. Distress, including respiratory stridor, was promptly relieved by probing the lumen to the balloon tube with a knitting needle. Subsequent splenorenal anastomosis was carried out. There has been no recurrence of hemorrhage since surgical treatment.

CASE 5.—A 37-year-old man was hospitalized with recurrent hemorrhage from esophageal varices secondary to Laennec's cirrhosis. Bleeding was previously controlled with tamponade, but on this occasion bleeding recurred each time tamponade pressure was released. Finally, pressure was maintained at 35 to 40 mm. Hg for eight days. Despite pressure, exsanguination occurred. Autopsy revealed varices and ulcerations of the esophagus linearly for 2 to 4 cm. at the site of esophageal balloon pressure in the lower one-third of the esophagus.

COMMENT

The greatest number of complications [3a] have been noted to be due to the placement of traction on the tube in an attempt to control bleeding not otherwise control-

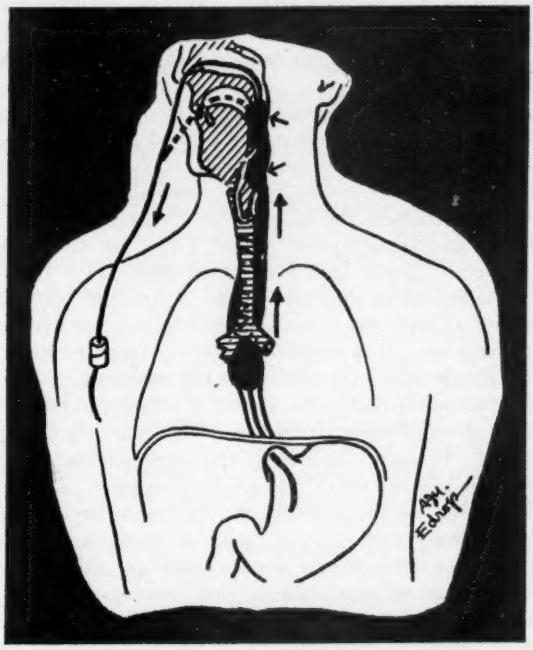

Fig. 3.—Compressive obstruction of airway when tube is inadvertently pulled up with balloons inflated. Top arrow shows point of obstruction in posterior pharynx. Dotted line indicates the alternate oral route of insertion.

lable, or to a misunderstanding leading to the routine use of traction. This complication has been that of the upward displacement of the tube and inflated esophageal balloon into the posterior pharynx, where its lodgement obstructed the air passage, as illustrated in Cases 1 and 2 above.

Case 1 represents our sole death. In this case asphyxia from the balloon obstructing the upper airway was a contributory cause of death. It is suggested that this can be avoided by (1) avoidance of traction except when essential in continued bleeding, (2) regulation of degree of tension by application of weights rather than by elastic traction, (3) regulation of distance through which traction can act by placing the weights a small distance above the floor or table, and (4) strict

supervision of patients by personnel instructed in management of the emergency situations that can arise. It has been suggested that short traction between the tube at the nares and the adhesive strapping at the chin might provide sufficient traction and yet give a short distance through which the traction can act. However, we have not attempted to use this method. With its use, the tube could not be pulled up far enough to obstruct the airway.

Case 2 represents the same complications as Case 1 but demonstrates a rapid and efficient method of handling the situation. Rapid transection of the tube with scissors deflates both the gastric bulb and the esophageal balloon, allowing for immediate correction of respiratory obstruction and easy removal of the tube.

Case 3 demonstrates that the complication of slippage can occur without traction. The contribution of the hiatus hernia to the ease of regurgitation is a matter of speculation but worth while keeping in mind, and patients with such hernias should be watched carefully.

Case 4 demonstrates that care should be taken by direct observation to ascertain that both gastric and esophageal balloons are deflated prior to removal. The tube should slide out easily. If it does not, probing of the tube lumina is indicated. That rebleeding did not occur during forceful removal is surprising.

Our last case demonstrates the complication of ulceration of the esophagus by pressure from the esophageal balloon. Case 3 may likewise demonstrate such ulceration, but previous peptic erosion had been present. We have not seen this complication often enough to state how it can be avoided. Other patients have tolerated pressures as high and tamponade as long as these patients without the occurrence of ulceration. It is suspected, however, that limitation of tamponade to 72 hours will greatly reduce the chances for this complication. Lower pressures, if effective in controlling bleeding, may also be of aid in prevention.

Another type of complication in the use of this tube was anticipated, but has never materialized. It seemed most likely that some attendant or relative would give the patients fluids orally with the tube inflated in place. Resulting backing up of fluids into the pharynx and overflow into the respiratory tract could result at least in aspiration pneumonia and conceivably in asphyxia. This is particularly dangerous, as some of these patients are semicomatose. Fortunately this has not happened at our institution.

It is to be reemphasized that no attempt is made to discourage the valuable emergency use of esophageal tamponade in bleeding varices of the esophagus. Our own immediate mortality from hemorrhage has been halved since this tube has been used. Savings of whole blood, limitation of subsequent serum hepatitis, and limitation of liver damage due to shock are additional advantages. We wish merely to report our experience with complications from the use of the tubes and to advocate some precautions and remedies.

SUMMARY

Five cases are described which represent the complications in the use of an esophageal compression tube (Sengstaken tube). Complications consisted of (1) posterior pharyngeal obstruction with or without traction on the tube; (2) failure of gastric balloon to deflate during removal, and (3) ulceration of the esophagus. Methods of avoiding complications are recommended. No attempt is made to detract from the proved usefulness of this type of tube.

VIRUS INFLUENZA A' INFECTION WITH PULMONARY MANIFESTATIONS

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AND
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FEW REPORTS of clinical pulmonary infiltration in uncomplicated virus influenza have been published,[1] and one [2] has appeared on a series in which there was secondary pulmonary involvement in many of the cases. In only two of these reports [3] were virus studies presented to confirm the etiological agent. It is the purpose of this paper to describe a benign pulmonary infiltration observed in a high proportion of patients in a recent epidemic of proved influenza. An attempt is made to compare the clinical manifestations in the group with infiltration and in that without infiltration, to provide further data on the relation of this infiltration to secondary bacterial pneumonia, and to discuss the effect of chemotherapy upon both groups.

METHODS

Eighty-two patients were referred to the U. S. Naval Hospital, Philadelphia, from the Receiving Station and ships of the Philadelphia Navy Yard, and 24 from other military and civilian sources in and about Philadelphia, with the clinical diagnosis of "influenza" during the period from Jan. 1 to the end of March, 1951. A ward was quickly set apart at the Naval Hospital to handle this acute problem. Thus, close daily observation was permitted on a group composed primarily of young adults who were without previous known exposure to or vaccination against influenza.

Total leucocyte and differential counts were performed on admission, daily for the next two days, and thereafter as indicated. Throat and sputa cultures were examined for common pathogenic bacterial flora of the respiratory tract; aerobic blood cultures were made as often as indicated. Roentgenograms of the chest were taken on admission; lateral views were made within one or two days and repeated weekly, or oftener if indicated. Blood Kahn examinations and urinalyses were routine on admission.

Throat washings were taken from 13 of the earliest arrivals and inoculated into the chick embryo by the amniotic route after prior treatment with penicillin (500 units per cubic centimeter) and streptomycin (250 units per cubic centimeter). A strain of influenza A' virus was

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The opinions expressed in this paper are those of the authors and do not reflect the policy of the Navy Department.

1. Stuart-Harris, C. H.; Andrewes, C. H.; Smith, W.; Chalmers, D. K. M.; Cowan, E. H., and Hughes, D. L.: A Study of Epidemic Influenza, with Special Reference to the 1936-1937 Epidemic, Medical Research Council Special Report Series No. 228, London, His Majesty's Stationery Office, 1938. Hodges, R. L.: Primary Influenzal Pneumonia, Air Surgeon's Bull. **1**:18, 1944. Bowen, A.: Acute Influenzal Pneumonitis, Am. J. Roentgenol. **34**:168, 1935.

2. Scadding, J. G.: Lung Changes in Influenza, Quart. J. Med. **6**:425, 1937.

3. Footnote 1. Scadding.[2]

isolated from several of these washings.[4] Sera were drawn on admission and weekly thereafter for as long as the patients were available; the samples were tested by the complement-fixation method summarized by Wiener and associates[5] and by Sigel[6] in an effort to demonstrate specific antibody-titer rises against influenza A and A′ antigens. The criterion for a positive diagnosis of influenza was a fourfold rise in antibody titer. Complement fixation of the Lee strain was carried out simultaneously.

Cold-agglutination and heterophile-antibody titers were determined on admission and after the 10th day of disease. Streptococcal antihemolysin and antihyaluronidase and pneumococcal antihyaluronidase titers were determined in a number of cases according to the technique of Harris.[7]

Other studies performed, when indicated, included determination of the icteric index, prothrombin time, total and fractional proteins, total chloride, carbon-dioxide-combining power, serum amylase, and thrombocyte count. In those cases in which extrasystoles, tachycardia, or substernal pain was pronounced, an electrocardiogram was taken; in those in which there were persistent headache and signs of meningeal irritation, a spinal tap was done.

The diagnosis of influenza virus infection was accepted when the following criteria were met: (1) presence of serological evidence of recent infection by the influenza virus; (2) demonstration of a clinical course compatible with such infection; (3) absence of bacterial pathogens as etiological agents.

One hundred six patients were admitted with the clinical diagnosis of "influenza," representing 31% of the total admitted with respiratory disease for the first three months of 1951. Of these, 13 patients were not admitted to the ward designated for influenza patients and

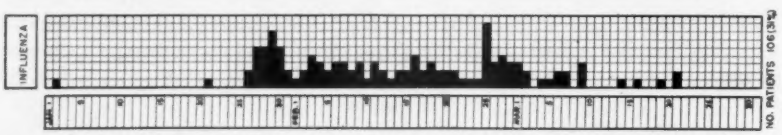

Fig. 1.—Graph showing daily incidence of admissions for influenza.

consequently could not be observed by us through the course of the disease. Ten were excluded because of inadequate serological data. Seven others were not included in the study because of concurrent bacterial infection or because a bacterial etiological agent could not be definitely eliminated.

RESULTS

The admissions for respiratory diseases from Jan. 1 to March 31, 1951, are shown in Table 1. These will be commented on later.

4. (*a*) All virus studies were conducted in the Virology Laboratory of the Children's Hospital, Philadelphia, under the direction of Dr. M. Michael Sigel (Sigel, M. M., in Influenza Viruses Identified, Medical News, J. A. M. A. **145**:574, 1951). (*b*) The streptococcal and pneumococcal antibody studies were performed through the courtesy of Dr. T. N. Harris, of the Children's Hospital, Philadelphia.

5. Wiener, M.; Henle, W., and Henle, G.: Studies on the Complement Fixation Antigens of Influenza Viruses Types A and B, J. Exper. Med. **83**:259, 1946.

6. Sigel, M. M.: Differences in Hemagglutinating and Antigenic Properties of Strains of Influenza Virus Isolated from One Outbreak, J. Immunol. **62**:81, 1949.

7. Footnote 4*b*. Harris, S., and Harris, T. N.: Measurement of Neutralizing Antibodies to Streptococcal Hyaluronidase by the Turbidimetric Method, J. Immunol. **63**:233, 1949. Harris, T. N.: Studies in the Relation of Hemolytic Streptococcus to Rheumatic Fever: III. Complement Fixation Versus Streptococcal Nucleoproteins with Sera of Patients with Rheumatic Fever and Others, J. Exper. Med. **87**:57, 1948; IV. Streptococcal Anti-Hyaluronidase (Mucin-Clot-Prevention) Titers in the Sera of Patients with Rheumatic Fever, Streptococcal, Am. J. M. Sc. **217**:174, 1949.

Controlled data on 76 patients with clinical influenza were obtained. Of these, 24 (31.6%) presented pulmonary infiltration. The average age of the entire group considered was 26.5 years, with 51 patients between 21 and 30 years of age, 13 between 17 and 20, 6 between 31 and 40, 3 between 41 and 50, and 3 over 50. The average age of those with infiltration was 22.3 years; 19 were between 18 and 30; 4 were between 31 and 40; and 1 was 63 years old. Of 31 patients treated with antibiotics, 14 had infiltrations and were given terramycin. The average period

TABLE 1.—*Admissions for Respiratory Diseases from Jan. 1 to March 31, 1951*

	Influenza	Common Cold; Acute Bronchitis	Bacterial Pneumonia	Acute Tonsillitis	Atypical Pneumonia
January	26	5	18	36	25
February	64	24	29	23	19
March	16	2	13	14	9
Total	106	31	60	73	53

TABLE 2.—*Symptoms in Seventy-Six Patients with Influenza*

	Patients With Infiltration		Patients Without Infiltration	
	No.	%	No.	%
Cough	24	100	37	71.1
Headache	8	33.3	21	40.4
Retro-orbital ache	11	45.8	19	36.5
Muscular pain	16	66.7	29	55.7
Nausea	3	12.5	3	5.8
Vomiting	1	4.2	1	1.9
Rhinorrhea	9	37.5	31	59.6
Substernal pain	3	12.5	4	7.6
Pleural pain	9	37.5	6	11.5
Chills	18	75.0	22	42.3
Fever	24	100	45	86.5
Blood-streaked sputum	7	29.2	2	3.8
Photophobia	1	4.2	1	1.9
Anorexia	21	87.5	38	73.0
Malaise	23	95.8	49	94.2
Anergy	21	87.5	42	80.7
Fitfulness	18	75.0	46	88.5
Epistaxis	0	0.0	1	1.9
Total number	24		52	

of hospitalization for those without infiltration was 13.2 days, and for those with infiltration, 17.6 days.

Symptoms.—The onset was sudden in 59 (77.6%) and gradual in 17 (22.4%). The average duration of symptoms before admission was 18 hours. Initial symptoms appeared to be "upper respiratory," including watery nasal discharge, turgidity, and sore throat, in 21 (27.6%); "lower respiratory," including cough generally nonproductive at first, chest pain especially on breathing, and agitated respiration, in 36 (47.4%), or "constitutional," including headache, malaise, anorexia, chills, muscle pain, fitfulness, and anergy, in 19 (25%). The original complex was quickly compounded in most cases by the addition of one or both of the other components. Table 2 compares the individual symptoms in those with and in those without infiltration.

Constitutional symptoms corresponded to the course of fever and cleared in an average of two days. The duration of the upper respiratory symptoms averaged five days and that of lower respiratory symptoms seven days in those without infiltration. In those with infiltration lower respiratory symptoms persisted an average of 11 days.

In those with roentgen manifestations, cough was generally severer and harsher, although the character and quantity of the sputum were similar to that in the group without infiltration. Of the nine who had blood-streaked sputum, seven (9.2% of the entire group) had evidence of infiltration. Of the 15 who had pleural pain, either diaphragmatic or lateral thoracic, 9 had infiltrations.

The temperature on admission varied from normal to 105 F. and averaged 101.3 F., while the average of the maximal temperature readings was 102.5 F., for the entire group. The maximum temperature of 69 (90.8%) was between 99 and 104 F.; for 7 (9.2%) there was no temperature reading above 99 F. through the course of the disease. In 61 (80.3%) the temperature returned to normal within

TABLE 3.—*Physical Findings in Seventy-Six Patients with Influenza*

	Patients With Infiltration		Patients Without Infiltration	
	No.	%	No.	%
Pharyngitis	16	66.7	37	71.1
Rhinitis	11	45.8	46	88.5
Fine rales	24	100	8	15.4
Coarse rales	14	58.3	1	1.9
Dulness	18	75.0	3	5.8
Diminished breath sounds	15	62.5	5	9.6
Bronchial breath sounds	4	16.7	1	1.9
Pleural friction rub	2	8.3	0	0.0
Dyspnea	1	4.2	0	0.0
Conjunctival injection	17	70.8	23	44.2
Florid facies	5	20.8	13	25.0
Total number	24		52	

three days; in 9 (11.8%) within five days; in 4 (5.3%), within 7 days, and in 1 within 9 days; in one the fever lingered remittently for 11 days. In 7 patients (9.2%) a secondary rise in temperature appeared on the third to fourth day but was unsustained, and the temperature returned quickly to normal. In one patient an infiltration which had not been present two days before appeared in the right cardiophrenic angle on a roentgenogram made after the secondary bout. There was no other correlation between the uncomplicated infiltrations and a second rise in temperature. Resolution occurred by lysis in 60 (78.9%) and by crisis in 9 (11.8%).

The pulse rate ranged from 72 to 136 and averaged 100 for the entire group on admission. Twenty-two (28.9%) of the entire group demonstrated a relative bradycardia. Blood pressures ranged from 92/56 to 168/98 and averaged 118/82 on admission, varying little through the course of the disease.

Physical Signs.—Table 3 shows physical findings in the group with and in that without infiltration. On admission, upper respiratory signs were present in 57 (75%), lower respiratory signs, in 38 (50%), and constitutional signs, in 62

(81.6%). The constitutional signs cleared within three days in 67 (88.1%), and the upper respiratory signs cleared within five days in 55 (72.4%). Lower respiratory signs cleared within four days in 29 (55.7%) of those without infiltration. In those with infiltration lower respiratory signs cleared within 10 days in 15 (62.5%), within 12 days in 21 (87.5%), and within 14 days in 24 (100%) by clinical signs.

On admission, pulmonary signs were present in 15 (62.5%) cases and positive roentgenograms were obtained in 21 (87.5%) of those with infiltration. Within three days of admission, correlation between those with physical and those with roentgen findings was possible in all but three patients, in one of whom infiltration succeeded a second bout of fever on the fourth day. Among those without roentgenographic evidence of infiltration on admission, physical signs appeared in 9 (17.3%) of the 52 who did not display clear-cut roentgen manifestations during the course of the disease. These signs disappeared in eight (88.8%) of these within three days.

TABLE 4.—*Incidence of Positive Throat Cultures Throughout Hospital from Jan. 1 to March 31, 1951*

	January	February	March	Total
Staph. aureus	12	21	35	68
Hemolytic Staph. aureus	1	11	21	33
Staph. albus	16	10	9	35
Beta hemolytic Streptococcus	6	18	11	35
Alpha Str. viridans	32	21	15	68
D. pneumoniae	4	4	6	14
H. influenzae	1	..	4	5
K. pneumoniae	1	..	..	1

LABORATORY RESULTS

Pneumococci were isolated from the sputum of one patient with an infiltration who was excluded from the series because of the possibility that these organisms were the etiological agent. Beta hemolytic Streptococcus was isolated from the throats of four patients during a second wave of admissions from Feb. 25 to March 4 and once outside this period. In one of these patients pulmonary infiltration was also present.

Staphylococcus aureus was found much more frequently during the final phases of the epidemic. It was discovered in the throats of three of those with infiltration and in the throats of 12 patients without infiltration on roentgenogram. The hemolytic form became more frequent also at that time, occurring in five of those without infiltration.

These tendencies paralleled the incidence of positive throat cultures throughout the hospital generally and may be summarized as follows: Staph. aureus was cultured 13 times in January, once in the hemolytic form; 32 times in February, 11 times in the hemolytic form, and 56 times in March, 21 times in the hemolytic form. Beta hemolytic Streptococcus was cultured 6 times in January, 18 times in February, and 11 times in March. The reverse of these trends were apparent for Staphylococcus albus and Streptococcus viridans. Staph. albus was found 16 times in January, 10 times in February, and 9 times in March. Alpha Str. viridans was found 32 times in January, 21 times in February, and 15 times in March. Diplococcus

pneumoniae was found four times in January, four times in February, and six times in March. Klebsiella pneumoniae (Friedländer's bacillus) was cultured once in February, and Hemophilus influenzae, once in January and four times in March. These findings will be commented upon later (Table 4).

The leucocyte counts ranged from 3,000 to 27,000 on admission and averaged 11,900. Counts averaged 8,800 on the second day, with a range from 3,800 to 18,400, and 11,300 on the third day, with a range from 4,300 to 26,000. Of those with infiltration, nine (37.5%) did not have counts over 9,000 during the period of hospitalization. Of those without infiltration, 19 (36.5%) did not have a count above 9,000 at any time during hospitalization. The differential white blood cell count ranged from 4 to 60 lymphocytes, with an average count of 31, and from 40 to 94 polymorphonuclear cells, with an average count of 70 on admission for the entire group. In five (20.8%) of those with infiltration and in nine (17.3%) of those without infiltration, there was a moderate lymphopenia during the first day of disease.

TABLE 5.—*Influenza and Cold-Agglutinin Determinations in Seventy-Six Patients*

	Patients With Infiltration	Patients Without Infiltration
Number with positive influenza titer	16	45
Number with negative influenza titer	4	7
Number with negative cold-agglutinin titer (<40 to 80)	16	35
Number with questionable cold-agglutinin titer (160)	3	2
Number with positive cold-agglutinin titer (320 or higher)	3	1
Total number	24	52

SEROLOGICAL FINDINGS

The etiological basis of the epidemic was established by the recovery and typing of a strain of influenza A′ virus from pooled throat washings of 13 patients and the subsequent demonstration of fourfold rises in titer of influenza A and A′ antibodies in paired serum specimens.[8] Sixteen (66.7%) of the patients with infiltration and 45 (86.5%) of those without were felt to have antibodies positive for influenza A′ virus. Four patients (16.7%) with clinical evidence of influenza and infiltration had no titer rises for influenza virus, and in four others (16.7%) titer rise was not demonstrated. Of those without infiltration, seven (13.5%) had no titer rises for influenza A and A′. In 16 (66.7%) patients with infiltration, no titer rise to cold agglutinins was found; 3 (12.5%) had questionable rises in cold agglutinins; three others (12.5%) showed positive rises and in 2 (8.3%) the cold-agglutinin rise was not demonstrated. Of those without infiltration, cold agglutinins were not found in 35 (67.3%), were questionable in 2 (3.8%), were present in 1 (1.9%) and were not demonstrated in 13 (25.0%) patients. Rises to influenza A and A′ viruses occurred after the ninth day (see Table 5).

In 33 persons, 23 (44.2%) without and 10 (41.7%) with infiltration, streptococcal and pneumococcal antihyaluronidase titers demonstrated no significant rise in

8. Hummeler, K.; Kravis, L. P., and Sigel, M. M.: A Rapid Method for the Identification of Influenza Viruses, to be published.

paired specimens. Streptococcal antihemolysin titers of 1:128 or above in single specimens were present in 10 (19.3%) patients without infiltration and in 3 (12.5%) with infiltration (Table 6).

The heterophile-antibody determination was not positive in any instance. Complement-fixation tests for antibodies to Coxiella burnetii (Rickettsia burneti) and the psittacosis-lymphogranuloma group of viruses carried out on those patients with negative titers for influenza did not demonstrate a diagnostic rise. The homogeneous nature of the group during a period of epidemic and the lack of contact with birds or animals make these possibilities unlikely.

OTHER STUDIES

Although studies to uncover involvement of the liver, pancreas, and spleen were made in the face of suggestive clinical evidence, no clear confirmation was apparent from the icteric index, prothrombin time, total and fractional protein levels, serum amylase value and thrombocyte counts. Fluid balance remained within normal limits in all patients observed, although moderate dehydration paralleled fever in 15

TABLE 6.—*Antihemolysin and Antihyaluronidase Determinations in Thirty-Three Patients*

	Patients With Infiltration	Patients Without Infiltration
Streptococcal antihemolysin titer of 128 or higher	3	10
Streptococcal antihyaluronidase titer of 128	1	2
Pneumococcal antihyaluronidase titer of 128 or higher	0	0
No change in antihemolysin or either antihyaluronidase titer	7	15
Total number	10	23

instances. Albuminuria with or without fever was not encountered in this series, although urinary concentration above 1.030 corresponding to fever was apparent in 12 patients. In four instances of meningismus, spinal taps showed cell counts and chemical values to be within normal limits. Electrocardiograms were performed for eight patients, three with frequent extrasystoles, one with tachycardia, and four complaining of severe substernal pain persistent for 12 hours or longer. All tracings were within normal limits, with the exception of that of one of the last patients, who was found to have first-degree heart block which was present one month later and may very well have predated his influenza. In three patients, one of whom had bronchitic-type infiltration, a transient 2+ Kahn reaction was present on single determinations but did not persist. In three patients atypical lymphocytes were observed on the differential blood smear on admission.

GENOGRAPHIC FINDINGS

The roentgenographic findings were considered in accordance with the classification of Lewis and Lusk.[9] Of a total of 24 patients with infiltration, 11 (45.8%) demonstrated bronchitic lesions denoted by increased density of one or both hilar shadows, with prominent bronchovascular markings extending from the hili. Seven (29.2%) had peribronchitic lesions extending into the cardiophrenic angle and out-

9. Lewis, E. K., and Lusk, F. R.: Roentgen Diagnosis of Pulmonary Atypical Pneumonia, Radiology **42**:425, 1944.

ward into the lung with peribronchial infiltrations, not completely obscuring the linear markings. In five (20.8%) the infiltrations were alveolar, obscuring the linear markings with denser peribronchiolar infiltrations variable in size, shape, and location. In one (4.2%) a denser consolidation was apparent fanning out into the parenchyma from the hilus, suggestive of lobar consolidation.

The distribution of the lesions was evaluated on the basis of sectoral location,[10] determined by dividing each hemithorax into three parts. The upper third included the hemithorax from the apex of the lung to the angle of Lewis, the middle third, the region from the angle of Lewis to the costochondral junction of the fourth rib, and the lower third, the area below this boundary. Two or more sectors were involved in 13 patients (54.1%). The lesions were predominantly in the lower sector in 11 patients (45.8%), in the lower left sector in 8 (33.3%), in the right middle sector in 7 (29.2%), and in the left middle sector in 9 (37.5%); apparently the upper sector was not involved at all. Involvement in the cardiophrenic angles predominated in frequency, with eight (33.3%) showing lesions on the right and five (20.8%) on the left.[11] On lateral projection these could be tentatively localized to the posterior basal segments of the lower lobes.[12] In three (12.5%) the infiltration appeared in the costophrenic angle on each side. In three (12.5%) the infiltration appeared to be localized to the lingular portion of the left upper lobe. This was the only upper lobe involvement encountered. The four cases reported below illustrate the essential findings that were prominent among those with infiltration.

REPORT OF CASES

Case 1.—A 20-year-old white youth was admitted to the hospital Feb. 9, 1951, after the sudden onset of malaise, muscle ache, chills, elevation in temperature to 103 F. and frontal headache, progressive over the preceding 12 hours. On admission his temperature was 102.2 F., the pulse rate, 84, and the respiration rate 20; he appeared uncomfortable with a flushed, anxious face, mild thin watery nasal discharge, turgid mucosae of nose, and injected fauces and pharyngeal walls. Mild, dry cough was present, which became harsh and productive on the second day of a thin yellowish sputum persisting for eight days. The leucocyte count was 12,800 with 76% neutrophiles and 18% lymphocytes. The cold-agglutinin titer was <4, and the complement-fixation titer was 1:64 for influenza A′ on the 10th day. Sputum culture on the third day gave no growth; a throat culture grew out Str. viridans and diphtheroids. A roentgenogram made on admission showed increased bronchovascular markings bilaterally with peribronchitic and alveolar-type infiltrations along the left cardiac border. The patient received 500 mg. of terramycin on admission and 250 mg. every 6 hours for 72 hours, along with symptomatic therapy. Rales at the base of the left lung were audible by the third day, and minimal percussion dulness was present. Resolution began on the 4th day and progressed to completion on the 11th day.

Case 2.—A 19-year-old white youth was admitted to the hospital Feb. 5, 1951, eight hours after sudden onset of weakness, chilliness, nausea, restlessness, irritability, and retro-orbital ache on eye movement. Examination revealed conjunctival injection, redness of nasal and faucial mucosae, hot dry skin, and slight nonproductive cough. His temperature was 102 F., pulse rate, 80, blood pressure, 120/88, and respiration rate, 22. The white blood cell count on admission was 8,200, with 67 polymorphonuclear forms and 25 lymphocytes per 100 cells on differential

10. Jordan, W. S.; Albright, R. W.; McCain, F. H., and Dingle, J. H.: Clinical Variations in Primary Atypical Pneumonia, Am. J. Med. **10**:3, 1951.

11. Dingle, J. H., and others: Primary Atypical Pneumonia, Etiology Unknown, War Med. **3**:223, 1943.

12. Chrysler, W. E.: Segmental Distribution of Primary Atypical Pneumonia, Am. J. Roentgenol. **56**:324, 1946.

count. No signs of chest involvement were evident on physical examination. A roentgenogram showed bronchitic and peribronchitic infiltrations bilaterally in the middle and lower thirds, especially in the left lower sector. On the third hospital day, pleuritic-type pain appeared in the left lower chest area, which cleared in 24 hours. Throat culture on the second day showed Staph. albus, Str. viridans, and diphtheroids; sputum was sterile on the second, third, and fourth days. The cold-agglutinin titer was < 4 on the 12th hospital day; the complement-fixation titer on the ninth hospital day was 1:32.

Case 3.—A 23-year-old white man was admitted to the hospital on Feb. 16, 1951, after onset of chills, fever, frontal headache, malaise, tiredness, muscle aches, and restlessness. He complained

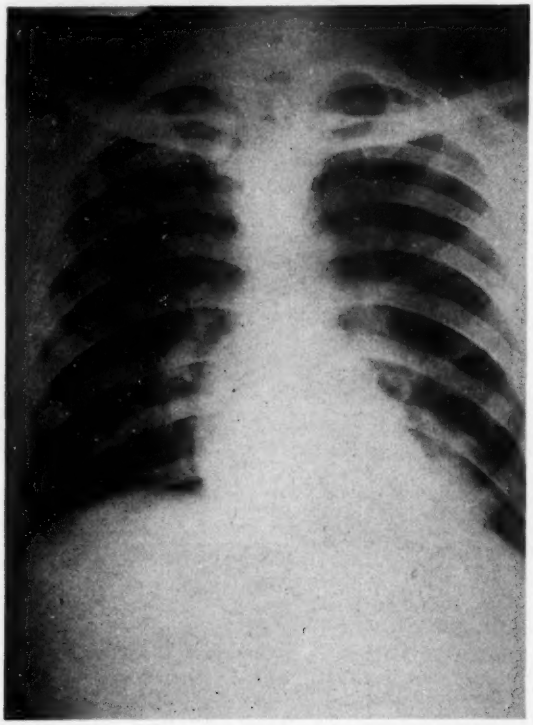

Fig. 2 (Case 1).—Exaggeration of hilar root shadows and perihilar bronchovascular markings with a small area of parenchymal infiltration in left cardiophrenic angle.

of pain anteriorly in the left fourth interspace on breathing. His temperature was 103 F. on admission, the pulse rate, 120, the respiratory rate, 24, and the blood pressure, 140/100. The white blood cell count was 5,100, with 74 polymorphonuclear cells and 22 lymphocytes per 100 cells. Fine crepitant rales were present in the fourth interspace anteriorly and at the base posteriorly, with slight percussion dulness anteriorly. A roentgenogram revealed fine bronchitic and peribronchitic infiltrations in the middle and lower sectors. Paroxysmal cough was present on admission and by the third day was productive of white to yellow sputum which was slightly blood-streaked. The infiltrate in the fourth interspace became denser and more alveolar in appearance by the 4th day, after which resolution began; the chest was clear roentgenographically on the 15th hospital day. The cold-agglutinin titer was 1:40 on the 10th day, and the complement-fixation titer for influenza A' rose from 1:8 to 1:128 at that time. Sputa and material from

the throat were negative for pathogenic flora. Terramycin, 500 mg. was given on admission and in doses of 250 mg. thereafter every six hours for four days with symptomatic therapy. The temperature was normal in 48 hours, and cough remitted by the 10th day.

CASE 4.—A 19-year-old white youth was admitted to the hospital Feb. 11, 1951, with malaise, anorexia, insomnia, headache, chilliness, and profuse sweating of 15 hours' duration. On admission the temperature was 100 F., the pulse rate, 106, the respiration rate, 22, and the blood pressure, 118/68. The total leucocyte count was 7,300, with 72% polymorphonuclear cells and 18% lymphocytes. The nasal mucosae and posterior pharynx were injected, and a thin watery

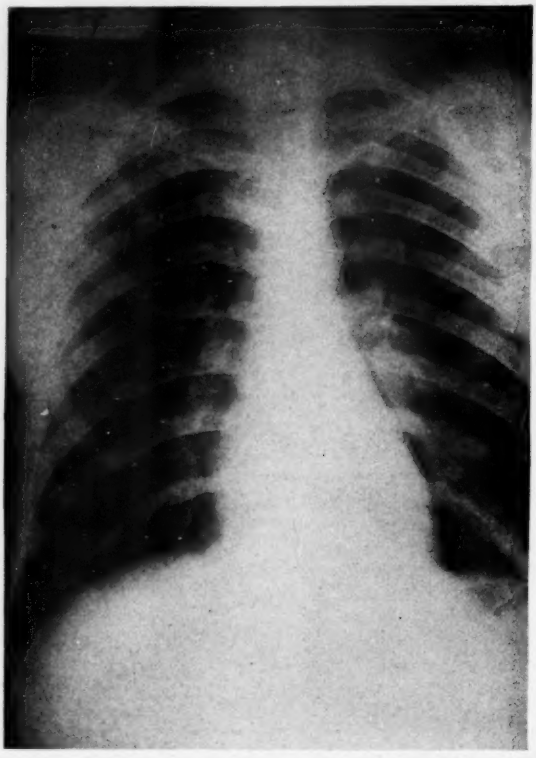

Fig. 3 (Case 2).—Prominence of both hilar shadows, with stringy bronchovascular fanning toward the bases and alveolar intensification in left subdiaphragmatic area.

discharge was present from the nose; the face was ruddy. Fine rales were present at the base of the right lung posteriorly. A roentgenogram showed diffuse middle and lower sector bronchitic infiltration and a peribronchitic infiltration in the right base. The cold-agglutinin titer was <4 on the 12th hospital day, and the complement-fixation titer was 1:128 at that time. Hoarseness appeared by the third hospital day. Fever declined in 36 hours but reappeared on the fourth hospital day, the temperature rising to 101 F. and returning to the base line in 12 hours. A paroxysmal cough became productive of yellowish sputum by the third day. Sputum and throat cultures were negative for pathogens. The cough cleared by the 10th day and the roentgen signs by the 17th day. Treatment was symptomatic.

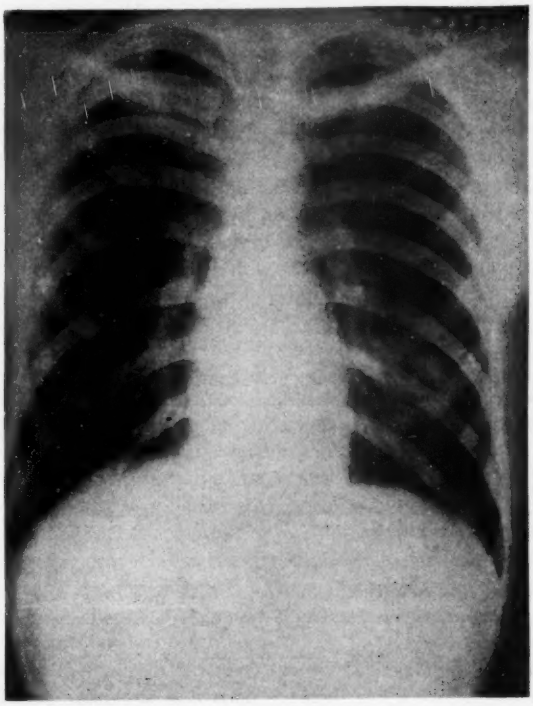

Fig. 4 (Case 3).—Hilar roots are prominent with perihilar bronchovascular striations extending into bases with area of parenchymal infiltration at left fourth anterior interspace.

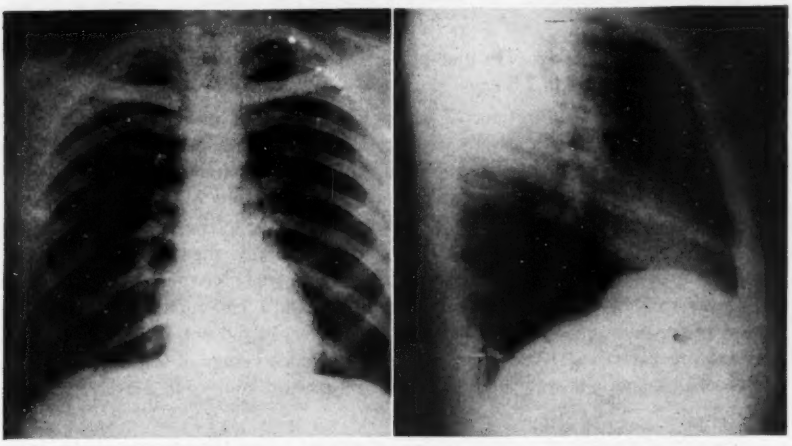

Fig. 5 (Case 4).—Minimal accentuation of right hilar root shadow, with small area of parenchymal infiltration at right cardiophrenic angle and accentuation of fine linear markings in left lower hemithorax.

TREATMENT

An attempt was made to evaluate the use of terramycin in the therapy of the disease. However, several other agents were also used for therapy. In all, 31 patients were given antibiotics for 48 hours or longer, and 41 did not receive antibiotics during the course of the disease. Two patients received antibiotics for less than 48 hours, and two, one of whom had an infiltration, received mixed antibiotic therapy and were, therefore, not included. The end-point of efficacy was the achievement of normal temperature and recession of constitutional symptoms. The average defervescence for those treated was 2.9 days, and, for those not treated, 2.3 days. Included in the latter group were those with normal temperatures on admission.

Fourteen of the patients with infiltration were given terramycin in doses of 500 mg. initially and 250 mg. every 6 hours for at least 48 hours. Defervescence in this

TABLE 7.—*Result of Treatment in Twenty-Four Patients with Influenza A' with Infiltration**

	(Temperatures Above 103 F.)	
	Controls	Terramycin
Defervescence (in days)	2.6	2.9
Patients	9	14

* One patient received mixed therapy.

TABLE 8.—*Result of Treatment in Twenty-Four Patients with Influenza A' with Infiltration**

	Controls					
	Temp. Below 102 F.†	Temp. Over 103 F.	Aureomycin	Penicillin	Chloramphenicol	Terramycin
Defervescence (in days)	2.0	2.6	2.8	2.6	3.4	2.4
Patients	18	14	6	5	5	1

* One received mixed antibiotics. Two received antibiotics less than 48 hours.
† Seven patients had no temperature reading above 99 F. during course of disease.

group occurred in 2.9 days. In nine patients with infiltration who were not treated defervescence occurred in 2.6 days.

Of those without infiltration, 17 were given antibiotics in adequate dosage and 32 were not treated. Of those treated, six were given aureomycin in doses of 500 mg. initially and 250 mg. very six hours for an average of four days; defervescence occurred in 2.8 days. In five who were given 200,000 units of crystalline aqueous penicillin three times a day for four days defervescence averaged 2.6 days. Five others who were given chloramphenicol, 500 mg. initially, then 250 mg. every six hours for four days, averaged 3.4 days of fever. One was given terramycin as above and fever cleared in 2.4 days. Of those untreated, 7 had no fever through the course of the disease, and, of 25 who did have fever, 11 did not at any time have a temperature exceeding 103 F. and defervesced in an average of 2.0 days, whereas 14 who had a temperature exceeding 103 F. returned to normal in 2.6 days (Tables 7 and 8).

The administration of antibiotics did not greatly affect the presence of the infiltrations, which persisted an average of 13.4 days in those treated and 15.1 days in those untreated. Once the constitutional symptoms were relieved, this group was

not markedly different from that without infiltration, except for roentgenographic findings and persistent minimal physical signs.

COMPLICATIONS

One patient, a 63-year-old white man with a normal roentgenogram on admission, showed full-blown right lower and middle lobe pneumonia with pleural effusion on the fifth hospital day, and his sputa yielded hemolytic Staph. aureus on two successive cultures. Blood culture was negative three times. It is interesting also that influenza titer rose from 1 : 8 to 1 : 128 by the 12th hospital day, and cold-agglutination titer rose from 1 : 40 to 1 : 1,280 by the 22d hospital day. A trial of 800,000 units of penicillin a day for 48 hours was made, but this failed to reduce the fever and white blood cell count, which rose in 36 hours from 28,000 to 40,000 with 98% polymorphonuclear cells, many containing toxic granulations. Terramycin was tried in 500-mg. doses every 4 hours for 24 hours, then in 250-mg. doses every 6 hours for three days longer, and was successful. After four days of the latter therapy, a monilial overgrowth appeared on the tongue of this patient, possibly secondary to his debilitation and the terramycin therapy.

In one patient, whose infiltration was more persistent and more symptomatic than the others, the chest was apparently clear on roentgenograms on the 19th day, at which time he had a cold-agglutination titer of 1,280 and still failed to demonstrate a rise in complement-fixation titer for influenza A' greater than the initial 1 : 8. It was necessary to readmit him eight days after discharge with a diagnosis of "atypical pneumonia" for what appeared to be a recurrence. Serological findings on this admission remained as before.

One patient without infiltration had typical follicular tonsillitis from which a beta hemolytic Streptococcus was cultured, and another from which no positive culture was obtained. Two patients had maxillary sinusitis and one frontal sinusitis. One patient required nasal packing for profuse bleeding from an erosion in Kiesselbach's triangle. One patient displayed transient urticaria from penicillin, which disappeared on discontinuance of administration of the drug; no other untoward results interfered with antibiotic administration.

COMMENT

The benign nature of influenza in this country since the 1918 pandemic has restricted the opportunity for close observation of the disease under hospital conditions largely to military installations.[13] This has been particularly true since the advent of accurate clinical methods of virus detection in influenza.[14] In institutions like the United States Naval Hospital, Philadelphia, early hospitalization has the added advantage of study prior to the development of secondary complications, which would be the more usual cause for hospitalization in civilian practice.

13. (*a*) Dingle and others.[11] (*b*) Chrysler.[12] (*c*) Kilbourne, E. D., and Loge, J. P.: Influenza A Prime: A Clinical Study of an Epidemic Caused by a New Strain of Virus, Ann. Int. Med. **33**:371, 1950. (*d*) Thalmann, W. G.; Kempe, C. H.; Worrall, J. A., and Meiklejohn, G.: Aureomycin in the Treatment of Influenza, J. A. M. A. **144**:1156, 1950.

14. Smith, W.; Andrewes, C. H., and Laidlaw, P. P.: A Virus Obtained from Influenza Patients, Lancet **2**:66, 1933. Smith, W.: The Complement-Fixation of the Virus of Influenza, ibid. **2**:1256, 1936. Hirst, G. K.: Adsorption of Influenza A Hemagglutinins and Virus by Red Blood Cells, J. Exper. Med. **76**:195, 1942.

Twenty-four (31.6%) of a group of 76 patients felt to have influenza A′ infection were found to have clinical and roentgenographic signs of pulmonary infiltration. The symptomatology alone was not sufficient to differentiate these from the rest of the group, although pleural pain and blood-streaked sputum, occurring in 9 (37.5%) and seven (29.2%), respectively, of those with infiltration, were notably more frequent than in those without infiltration. Physical signs, on the other hand, were of considerable help in the differentiation, appearing in 15 (62.5%) of those with positive chest roentgenograms on admission. In nine (17.3%) of those without infiltration on roentgenogram, physical signs were present on admission, an observation which has been noted by others.[15] In the latter instance, however, these signs disappeared in three days, at which time a high correlation between roentgenographic and physical findings was possible in those with infiltration.

From a laboratory standpoint, the presence of influenza was felt to be established in 16 (66.7%) of those with infiltration and in 45 (86.5%) of those without infiltration. A bacteriological search for agents responsible for the infiltrations did not provide any clear-cut pathogen. An attempt to cross check this serologically tended in 10 patients (41.7%) to confirm the absence of streptococcal and pneumococcal infection in the group. In 16 (66.7%) of those with infiltration and in 35 (67.3%) of those without infiltrations, the cold-agglutination test was negative. In one (1.9%) of those without infiltration and in three (12.5%) of those with infiltration, cold-agglutination titers were positive; in two (3.8%) of the former and three (12.5%) of the latter groups, they were questionably positive.

In this series of patients, no specific myocardial,[16] hypotensive,[17] or visceral[18] involvement was demonstrated. There were three instances in which transiently positive Kahn reactions were obtained and three in which more than five atypical lymphocytes were found on the differential count. In nine of those with infiltration a moderate lymphopenia was noted.[19]

In the use of the complement-fixation determination for influenza A and A′, the antibody response may fail to appear in 10 to 20% of those infected,[20] but the reliability of this test seems to be greater than that of the hemagglutination-inhibition

15. Scadding.[3] Jordan and others.[10] Meakins, J. F.: Primary Atypical Pneumonia of Unknown Etiology, Canad. M. A. J. **48**:333, 1943.

16. Finland, M.; Parker, F., Jr.; Barnes, M. W., and Jolliffe, L. S.: Acute Myocarditis in Influenza A Infection: 2 Cases of Non-Bacterial Myocarditis, with Isolation of Virus from Lungs, Am. J. M. Sc. **209**:455, 1945.

17. Chang, H.-T., and Kempf, J. E.: The Hypotensive Action of Influenza Virus in Rats, J. Immunol. **65**:75, 1950.

18. Henle, G., and Henle, W.: Studies on Toxicity of Influenza Viruses: I. The Effect of Intracerebral Injection of Influenza Viruses; II. The Effect of Intra-Abdominal and Intravenous Injection of Influenza Viruses, J. Exper. Med. **84**:623, 1946. Henle, W., and Henle, G.: Studies on the Toxicity of Influenza Viruses: III. Immunization of Mice Against the Toxic Activity of Influenzal Viruses; A New Potency Test for the Assay of Vaccines of Influenzal Virus, J. Immunol. **59**:45, 1948.

19. Harris, S., and Henle, W.: Lymphocytopenia of Rabbits Following Intravenous Injection of Influenzal Virus, J. Immunol. **59**:9, 1948.

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21. Vinson, J. W., and Walsh, F. T.: The Effect of Terramycin on the PR8 Strain of Influenza A Virus in Chick Embryos and Mice, J. Immunol. **65**:129, 1950.

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27. Harfold, C. G.; Lieder, V., and Hara, M.: Effect of the Lesion Due to Influenza Virus on the Resistance of Mice to Inhaled Pneumococci, J. Exper. Med. **89**:53, 1949.

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In the present series there were no deaths. The one bacterial pneumonic complication occurred in an elderly white man without pulmonary infiltration on admission. Among the other 43 initially untreated patients both with and without infiltration and the 35 treated patients of both groups, no other pulmonary complication appeared. The changing throat flora evident throughout the hospital and in the epidemic group might have been expected to increase the hazard of this complication, but it did not seem to do so. Since the group as a whole was primarily young and healthy, with an average age of 26.5 years, it is possible that age and previous state of health play important roles in the incidence of secondary pneumonia in influenza virus infection.

In certain cases of acute pyrexial onset in which symptoms and fever quickly subside, despite the presence of minimal benign pulmonary infiltration, which may persist as long as 15 days as a roentgen finding, and in the absence of adequate virus studies, the diagnosis of virus influenza infection should be strongly entertained.[29] The diagnosis "primary atypical pneumonia" might better be reserved for those more prolonged, remittently febrile, and debilitating cases in which causation remains unestablished.[30]

SUMMARY

Seventy-six cases diagnosed as influenza A′ were studied during a recent outbreak of the disease. In 24 of these (31.6%) infiltration was found roentgenographically and clinically. The possibility that these infiltrations were due to other etiological agents was examined. The cold-agglutination method did not aid in establishing the diagnosis. Serological responses to influenza A and A′ accompanying a clinical course compatible with this diagnosis tended to confirm the infiltrations as viral in origin. The clinical, roentgenographic, laboratory, and therapeutic features of this outbreak of influenza A′ are recorded.

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MUMPS ARTHRITIS

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THE OCCURRENCE of joint involvement during the course of epidemic parotitis has seldom been referred to in the medical literature. Several authors [1] merely mention arthritis among the complications of mumps. However, the subject is well discussed in a textbook by Jochmann,[2] and it is also commented on briefly in single case reports by Wilson [3] and Magida.[4] The present paper is based on our recent experience with four cases of mumps complicated by arthritis.

REPORT OF CASES

CASE 1.—L. R., a man aged 28, was admitted to the Willard Parker Hospital on Feb. 18, 1951, with a two-day history of swelling over the parotid glands and of abdominal pain and painful testicular swelling for one day. His past history was not remarkable.

Examination revealed a well-developed man who appeared uncomfortable because of the testicular pain. The temperature was 103.4 F., the pulse rate, 90, and the respiration rate, 20 per minute. The eyes, ears, nose, and throat appeared normal. Both parotid glands were swollen. The heart and lungs were normal. The abdomen was soft and not tender. There were swelling and tenderness of both testes, more marked on the left. The neurological examination revealed no abnormality. The urine was clear and showed a specific gravity of 1.020, a slight trace reaction for albumin, 2 to 3 white blood cells, 1 to 2 red blood cells, and an occasional epithelial cell. The blood Mazzini reaction was doubtful. The red blood cell count was 3,000,000, with 13 gm. of hemoglobin, and the white blood cell count was 9,900, with 65% polymorphonuclear cells, 33% lymphocytes, and 2% eosinophiles.

The clinical picture remained unchanged until the third hospital day, when some reduction in the parotid swelling was noted. At this time the patient began to complain of headache. There were, however, no signs of meningeal irritation. During the succeeding few days there

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2. Jochmann, G.: Lehrbuch der Infektionskrankheiten, Berlin, Julius Springer, 1924, p. 317.

3. Wilson, R. E.: Arthritic Purpura and Pancreatitis Following Mumps, Brit. M. J. **1**:784, 1926.

4. Magida, M. G.: Epidemic Parotitis Complicated by Pericarditis and Serositis, Ann. Int. Med. **35**:218, 1951.

was progressive improvement, with defervescence and complete subsidence of the parotid swelling and testicular symptoms by the seventh hospital day.

On the eighth hospital day the patient's temperature rose again to 101 F. At the same time the patient began to complain of severe pain in both upper extremities, with pain and limitation of motion in his shoulders and hands. There was no redness or swelling, but marked tenderness of the shoulder joints and the metacarpal and interphalangeal joints of both hands was present. Two days later the left hip joint became involved. The heart findings remained normal. The arthralgia failed to respond to treatment with acetylsalicylic acid, 60 grains (3.9 gm.) per day, and required administration of codeine and meperidine (demerol®) hydrochloride for relief. The erythrocyte sedimentation rate was 109 mm. in one hour.

From the 11th to the 17th hospital days the clinical picture was that of a migrating polyarthritis, with recession of the pain in the shoulders and involvement of the left knee, right wrist, both ankles, and the metacarpal and phalangeal joints. The degree of involvement varied, with some joints being only painful and tender and others also red and swollen. The temperature ranged between 100 and 101.4 F. The erythrocyte sedimentation rate remained elevated, with a reading of 120 mm. in one hour. There was also a slight leucocytosis, with 11,900 white blood cells, of which 68% were polymorphonuclear cells, 25% lymphocytes, and 7% eosinophiles. The mumps complement-fixation test gave a positive result on two occasions in 1:256 titer. Roentgenograms of the involved joints did not reveal any abnormal findings. Repeat serologic tests for syphilis all gave negative reactions. The electrocardiogram was normal.

On March 7, the 18th hospital day, there occurred an almost abrupt subsidence of all the arthritic manifestations, associated with a return of the temperature to normal. The patient remained asymptomatic and appeared completely recovered at the time of his discharge from the hospital on March 11, 1951.

In this case there was a classic picture of mumps, complicated early by orchitis and confirmed by the results of the complement-fixation test. On the 10th day of the patient's illness polyarthritis developed, involving small and large joints. The arthritis was associated with fever, slight leucocytosis, and elevated sedimentation rate. There was no clinical or electrocardiographic evidence of cardiac involvement. It is also to be noted that roentgenograms of the involved joints were entirely normal. The joint symptoms did not respond to acetylsalicylic acid therapy but subsided spontaneously within 10 days. It was felt that this patient's arthritis was definitely related to his mumps.

CASE 2.—J. H., a man aged 43, admitted to the Willard Parker Hospital on June 3, 1951, complained of bilateral parotid swelling, fever, headache, and generalized aches of one week's duration. On the evening before admission the patient also had painful swelling of the right testis. His past history was irrelevant.

Examination revealed a well-developed man, not appearing acutely ill. The temperature was 99 F., the pulse rate, 84, and the respiratory rate, 24 per minute. The eyes, ears, nose, and throat showed no abnormalities. Both parotid glands were moderately enlarged and tender. The lungs were clear. The heart was normal. There were no abnormal findings in the abdomen. The right testis was enlarged and very tender. The neurological examination revealed normal findings. The urine was clear and showed a specific gravity of 1.012, an occasional white blood cell, and a few epithelial cells, but gave negative reactions for albumin and glucose. The white blood cell count was 5,500, with 63% polymorphonuclear cells and 37% lymphocytes. The blood Mazzini reaction was negative.

In the evening of the first hospital day the temperature rose to 104.4 F. At the same time the swelling and tenderness of the right testis became more evident. On the third hospital day the patient began to complain of pain on motion in both shoulders and knees. These joints were tender but not swollen or red. The temperature on this day, however, was down to 101 F. The following day the arthritis extended to both wrists and ankles and the tarsometatarsal joints of the left foot. There was some radiation of the pain to the upper parts of the arms. A lumbar puncture yielded clear spinal fluid, with no cells and 25 mg. of protein, 79 mg. of sugar, and 711 mg. of chlorides per 100 cc. The erythrocyte sedimentation rate was 92 mm. in one hour.

The serum amylase was 368.5 units. The electrocardiogram was normal. A roentgenogram of the chest showed some increased bronchial markings but no other abnormalities.

On the fifth hospital day the temperature came down to 98.6 F. The parotid swelling had disappeared, and the testicular swelling had diminished. There were still pain in the shoulders and pain and tenderness on motion of the knees and right ankle. During the succeeding few days there was a gradual subsidence of the joint symptoms and the testicular involvement. The sedimentation rate on June 18 decreased to 36 mm. in one hour. The patient was discharged from the hospital on June 22 in excellent condition.

This patient presented on admission a definite picture of mumps associated with orchitis. Although no abdominal symptoms were present, the high serum amylase suggested pancreatic involvement. The polyarthritis appeared on the 10th day of the illness and involved predominantly the large joints. The clinical course was benign, and the arthritic symptoms subsided spontaneously within eight days. In this case the polyarthritis appeared clearly related to the mumps.

CASE 3.—A. T., a woman aged 27, was admitted to Bellevue Hospital April 21, 1951, with the chief complaint of painful swelling of the joints of three weeks' duration. The joint symptoms appeared first in the right wrist, elbow, and shoulder and in a short time extended to the left shoulder, both ankles, and both knees. The involved joints were swollen, red, and extremely tender. Swelling of the left parotid gland was noted on the day following the onset of the arthralgia. One week later, as the left parotid swelling began to subside, the right gland became enlarged and painful. These symptoms were accompanied with a low-grade fever. There was no history of a recent sore throat. The past history was irrelevant.

Examination revealed a well-developed young woman who did not appear particularly ill. The temperature was 100.6 F., the pulse rate, 88, the respiratory rate, 18, and the blood pressure, 102/70. The right parotid gland was swollen, enlarged, and tender. The lungs were clear. The heart was normal in size and contour, and no murmurs were audible. The abdomen was soft and nontender. There was pain on motion in both shoulders, ankles, and knees and in the right wrist and elbow, but no redness or conspicuous swelling was noted in these joints. Neurological examination gave entirely normal results. The red blood cell count was 4,340,000, with 14 gm. of hemoglobin. The white blood cell count was 9,550, with 73% polymorphonuclear cells, 17% lymphocytes, 8% monocytes, and 2% eosinophiles. The erythrocyte sedimentation rate was 110 mm. in one hour. The urine was entirely normal. Blood, urine, and cervical secretion cultures were all sterile. Heterophile, hemolytic streptococcal, and sheep-cell agglutinations were all negative. A blood amylase determination showed 222 units. There was a 4+ blood Wassermann reaction. The spinal fluid was clear and showed no cells, 12 mg. of protein and 90 mg. of sugar per 100 cc., and a negative Wassermann reaction. The electrocardiogram was normal. Roentgenograms of the chest, bones, and joints showed no abnormalities.

On the fifth hospital day the patient complained of severe pain in the left knee, in which a moderately large effusion developed. The following day there was evidence of synovial fluid in the right knee, both ankles, wrists, and elbows, and the interphalangeal joints. At this time the temperature rose to 106 F. The patient complained also of a headache and exhibited some nuchal rigidity. The spinal fluid, however, was normal. There was then a white blood cell count of 21,000, with 85% polymorphonuclear forms. The arthralgia was relieved somewhat with administration of codeine. Aspiration of the left knee joint yielded 30 cc. of clear, yellow, nonviscid fluid, with numerous polymorphonuclear cells. Smears and cultures of this fluid were negative for organisms. The mumps complement-fixation titer in the joint fluid was 1:16 on the eighth hospital day.

On the 12th hospital day, without any specific therapy, all the joint symptoms, as well as the parotitis, subsided. The temperature, which had fallen by lysis, became normal. A slight residual arthralgia persisted for a week and then cleared. The blood amylase dropped to 106 units. The serum complement fixation for mumps, which showed a titer of 1:16 on the eighth hospital day, rose subsequently to 1:256. The antistreptolysin O titer was 700 units per cubic centimeter. Repeated electrocardiograms were normal. Because of the positive blood Wassermann reaction, the patient was retained in the hospital for a course of antisyphilitic therapy. She was discharged, completely asymptomatic, on the 29th day.

In this case the polyarthritis appeared one day before the onset of the mumps and persisted for about five weeks. The arthritic involvement was extensive and associated with effusions, one of which was moderately large. It is of interest to note that the aspirated fluid showed numerous polymorphonuclear cells but yielded no organisms. All the joint symptoms subsided spontaneously, without recourse to any specific medication. While no abdominal symptoms were present, the blood amylase showed a moderate elevation. The significance of this is difficult to evaluate. Additional findings of note were a leucocytosis, an elevated sedimentation rate, a 4+ blood Wassermann reaction, and a strongly positive result on the mumps complement-fixation test. Cultures of the blood, urine, cervical secretion, and joint effusion were all negative. While the hemolytic streptococcal and sheep-cell agglutinations were negative, the antistreptolysin O titer was strongly positive. This, of course, raises the question of the possibility of rheumatic fever, the relation of which to a recent infection by the hemolytic Streptococcus is at present being amply supported by many investigators. However, as pointed out by Swift,[5] the occurrence in a patient's serum of antibodies against the extracellular components of the hemolytic Streptococcus merely indicates a previous infection with some strain belonging to this group of organisms. This author further emphasizes that even high antistreptolysin O titers may persist in a patient's serum for many months, possibly years, after the streptococcal disease and are not, therefore, definitely indicative of a recent streptococcal infection. Unfortunately, the patient failed to appear for a recheck of the antistreptolysin titer at a later date.

It may be further argued that the presence of polymorphonuclear cells in the joint exudate would tend to rule out a virus type of reaction. However, as noted by Rivers,[6] both the parotid gland and the duct exudates in mumps contain polymorphonuclear cells. It is also well known that in virus infections of the central nervous system, including mumps, the cellular reaction is occasionally of the polymorphonuclear variety.

It would seem to us that lack of clinical evidence of cardiac involvement and the normal electrocardiograms constitute, in good measure, arguments against a diagnosis of rheumatic fever. The negative streptococcal and sheep-cell agglutinations, as well as the clinical course, would seem to militate against a diagnosis of rheumatoid arthritis. At any rate, the relation in this case of the arthritis to the mumps appears very likely, though by no means certain.

CASE 4.—B. B., a man aged 40, was admitted to the Willard Parker Hospital on Aug. 6, 1951, with the complaint of bilateral parotid gland swelling of five days' duration. There was no history of a recent antecedent sore throat or any other respiratory infection. He denied venereal disease.

Examination revealed a well-developed man who did not appear acutely ill, but who was very uncomfortable because of the testicular pain. The temperature was 100.2 F., the pulse rate, 60, and the respiratory rate, 18 per minute. The blood pressure was 130/90. The eyes, ears, nose, and throat were normal. Both parotid glands were slightly swollen but not tender. The lungs were clear. The heart was normal. There was slight tenderness in the right upper abdominal quadrant, but there was no associated spasm. Both testes were swollen and tender, with greater involvement on the left. Results of the neurological examination were negative. The red blood

5. Swift, H. F.: The Etiology of Rheumatic Fever, Ann. Int. Med. **31**:715, 1949.

6. Rivers, T. M.: Viral and Rickettsial Infections of Man, Philadelphia, J. B. Lippincott Company, 1948, p. 405.

cell count was 5,150,000, with 13 gm. of hemoglobin, and the white blood cell count was 14,000, with 67% polymorphonuclear cells, 32% lymphocytes, and 1% eosinophiles. The urine showed no abnormality.

Treatment was palliative, consisting of the use of acetylsalicylic acid and the application of an ice bag to the scrotum. During the first two hospital days the patient's condition remained unchanged. On the third day he had nausea and headache, associated with a rise in temperature to 104 F. There were, however, no neurological signs suggestive of cerebral or meningeal involvement. Diethylstilbestrol therapy was then instituted, with a dosage of 15 mg. per day. This medication was continued for a four-day period, at the end of which time marked improvement in the symptoms became apparent. The fever, however, persisted.

On Aug. 15, the ninth hospital day, the patient had pain and tenderness over the posterior aspect of the lower portion of the left leg. This was followed by edema, redness, and tenderness of the left ankle, with marked limitation of motion in that joint. Pressure on the left calf also produced severe pain in the ankle. Soon the left knee joint became warm and tender but not definitely swollen. The patient's temperature was then 102 F. The heart remained normal. The erythrocyte sedimentation rate was 28 mm. in one hour. The throat culture showed a mixed flora, consisting of Staphylococcus aureus, hemolytic Streptococcus, and Neisseria catarrhalis. The electrocardiogram was normal. The result of a mumps complement-fixation test was positive in a titer of 1 : 128. The serum antistreptolysin O titer was 100 units per cubic centimeter, which is normal. Roentgenograms of the involved joints showed no abnormalities.

In order to investigate the effect of hormonal therapy on the arthralgic symptoms, the use of corticotropin (ACTH) was begun on Aug. 17. The hormone was administered intravenously for five consecutive days. The initial dose of the drug was 20 mg., and the subsequent dosages were 10 mg. per day for two days and 5 mg. daily for another two days. Following the first hormonal treatment, there was a dramatic improvement in all the symptoms, with defervescence and almost complete subsidence of the tendon and joint tenderness and of the ankle swelling. However, when the hormone treatment was withheld for two days, there were a moderate rise in temperature and a return of the arthralgic complaints, though to less degree. Administration of corticotropin was, therefore, resumed on Aug. 24 and continued for six days. This resulted again in striking clinical improvement. The erythrocyte sedimentation rate decreased to 13 mm. in one hour. The only side-effects from the hormonal therapy were euphoria, increase in appetite, and slight insomnia. At the time of his discharge from the hospital on Sept. 4, the patient was in very good condition, although he still had slight tenderness in the ankle. On follow-up observation three weeks after his discharge, the patient was able to walk without any difficulty.

This patient presented a definite picture of mumps, complicated by orchitis and confirmed by the result of a complement-fixation test. On the 14th day of his illness arthritis developed, involving two large joints and associated with tenosynovitis. There were also fever, moderate leucocytosis, and slight elevation of the erythrocyte sedimentation rate. The antistreptolysin O titer, however, was normal. In this case, it seems to us, there can be little doubt that the arthritis and tenosynovitis were related to the mumps.

Of special interest in this case was the use of corticotropin intravenously in accordance with the method recommended by Mandel and associates.[7] While the arthralgic symptoms responded dramatically to this drug, they recurred within two days following withdrawal of the medication. It may also be noted that the hormonal therapy did not foreshorten the total duration of the arthritis, which persisted in a minor form for about four weeks.

7. Mandel, W.; Singer, M. J.; Gudmundson, H. R.; Meister, L., and Modern, F. W. S.: Intravenous Use of Pituitary Adrenocorticotropic Hormone (ACTH): Report on Its Administration in 25 Cases, J. A. M. A. **146**:546, 1951.

COMMENT

It is apparent from this study that some cases of epidemic parotitis are complicated by arthritis. In Cases 1, 2, and 4 the arthritic complication was clearly related to the mumps. The relation between the joint involvement and the mumps in Case 3 is somewhat less certain, mainly because of the demonstration of a high antistreptolysin O titer in the patient's serum.

With regard to the pathogenesis of the arthritis, it is necessary to emphasize the present-day concept that epidemic parotitis is a generalized virus infection which is capable of affecting various parts of the body, including the joints. The commoner complications of mumps are orchitis, oophoritis, pancreatitis, and meningoencephalitis. Recently attention has been directed to the pericardial and myocardial complications of the disease. As pointed out by Magida,[4] it is likely that the joint involvement represents an inflammation of serous surfaces of the same character as that evidenced by pericarditis or orchitis.

Summary of Pertinent Clinical and Laboratory Data in Four Cases of Mumps Arthritis

Case No.	Sex and Age, Yr.	Character of Arthritis	Time Relation of Arthritis to Onset of Mumps	Duration of Arthritis	Pertinent Laboratory Findings	Comment
1	M 28	Large and small joints	10 days after mumps	10 days	Sedimentation rate, 109 mm./hr.; mumps complement fixation, 1:256; electrocardiogram normal	No relief with acetylsalicylic acid; spontaneous subsidence
2	M 43	Large and small joints	10 days after mumps	8 days	Sedimentation rate, 92 mm./hr.; later, 36 mm./hr.; spinal fluid normal; serum amylase, 368.5 units; electrocardiogram normal	Spontaneous subsidence
3	F 27	Large and small joints with effusions	1 day before mumps	5 wk.	Sedimentation rate, 110 mm./hr.; mumps complement fixation, 1:256; serum amylase, 222 units; antistreptolysin O titer, 700 units/cc.; spinal fluid normal; electrocardiograms normal	Some relief with codeine; spontaneous subsidence
4	M 40	Large joints with tenosynovitis	14 days after mumps	4 wk.	Sedimentation rate, 28 mm./hr.; later, 13 mm./hr.; mumps complement fixation, 1:128; antistreptolysin O titer, 100 units/cc.; electrocardiogram normal	Striking improvement while receiving ACTH

It is possible also that the arthritis is in the nature of an antigen-antibody reaction, similar to the mechanism proposed for the poststreptococcal diseases. The antigen in this instance would be the mumps virus. In this connection it may be noted that in three of our cases an interval of 10 to 14 days elapsed from the onset of the mumps to the appearance of the arthritis. It is conceivable that this interval represents the period during which the specific antibodies are formed.

As shown in the accompanying table, mumps arthritis presents no clinical features distinguishing it from other forms of infectious arthritis. As a rule, it takes the form of a migrating polyarthritis, involving both large and small joints. There may also be an associated tenosynovitis or collections of synovial fluid. While the arthritis may antedate the mumps, as noted in Case 3, it more commonly occurs 10 to 14 days after the appearance of the parotitis. The arthritic symptoms last one to several weeks and then subside spontaneously, without residuals. It may be noted that the use of corticotropin resulted in only temporary suppression of the arthralgic manifestations. A point of particular interest is the age factor in mumps

arthritis. It would seem from our cases and those recorded by Wilson [3] and Magida [4] that this complication occurs predominantly, if not exclusively, in young adults.

The arthritic complication of mumps must be borne in mind and must not be confused with rheumatic fever or other forms of infectious arthritis. Since the joint symptoms may antedate or occur possibly in the absence of frank parotitis, the difficulty of differentiating this form of arthritis from rheumatic fever is obvious. It is not unlikely that the arthritic complication of mumps is commoner than is generally supposed. From a practical point of view it is important to recognize that this form of arthritis is self-limited and thus avoid subjecting the patient to unnecessary therapy and to prolonged confinement to bed.

SUMMARY

Four cases of epidemic parotitis complicated by joint involvement are described. The relation between the mumps and the arthritis appeared clear in three of the cases and less certain in the remaining case. The possible pathogenesis and the clinical features of this form of arthritis are discussed.

ADDENDUM

Since this manuscript was submitted, one of us (E. A.) has observed an additional case of mumps arthritis.

On April 5, 1952, P. C., a man aged 47, was admitted to the Willard Parker Hospital with the complaints of fever and painful swelling of the testes of 4 days' duration and of swelling of both sides of his face for 10 days. The temperature was 103.8 F., the pulse rate, 94, and the respiratory rate, 28. The blood pressure was 120 systolic and 85 diastolic. There was slight swelling of both parotid glands and of the left submaxillary gland. The orifices of Stensen's ducts were edematous and injected. The heart and lungs presented no abnormal findings. The abdomen was soft and not distended or tender. Both testes were swollen, red, and tender. The neurological examination gave entirely normal results. The white blood cell count was 14,700, with 61% polymorphonuclear cells, 36% lymphocytes, and 3% eosinophiles. Urinalysis showed an occasional white blood cell but no other abnormality. The Mazzini reaction was negative. Nose and throat cultures revealed the presence of Staph. aureus, Staphylococcus albus, and hemolytic Streptococcus. The patient was treated with 600,000 units of procaine penicillin and 15 mg. of diethylstilbestrol daily and the use of a supporting scrotal bridge. Clinical improvement became apparent after several days of therapy.

On April 9, the fifth hospital day, the patient complained of pain in several joints. The right knee, the left shoulder, and the interphalangeal joints of the left hand were red, warm, swollen, and tender. The temperature was then 101 F. The joint pains did not respond to salicylate therapy and required opiates for relief. During the succeeding few days the arthritic manifestations extended to involve many of the large and small joints of all the extremities. The heart remained normal. The erythrocyte sedimentation rate was 85 mm. in one hour. The blood amylase was 82 units. The antistreptolysin O titer was 50 units per cubic centimeter. The mumps complement-fixation test was positive in a titer above 1:256. Roentgenograms of the shoulder, elbow, and knee joints revealed no changes, but those of the interphalangeal joints of the hands showed soft-tissue swelling. Serial electrocardiograms were all normal. The patient was treated with corticotropin intravenously, 10 mg. daily, for five days. Symptomatic improvement was prompt and striking. The arthritic manifestations, however, recurred when the hormonal treatment was discontinued. Resumption of the therapy resulted in dramatic improvement, and withdrawal of the drug was again followed by a return of symptoms. This clinical experiment was repeated four times, with the same results each time. The arthritic symptoms subsided spontaneously on April 27. Thereafter, the patient remained symptom-free and was discharged from the hospital on May 3. The erythrocyte sedimentation rate was 62 mm. at the time of discharge and dropped to 36 mm. in one hour two weeks later.

Dr. Marcel Tuchman assisted in the study of Case 4.

A CLINICAL STUDY OF GITALIN

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VARIOUS purified fractions of digitalis leaf have been prepared in the hope of improving its effectiveness in the management of cardiac decompensation. Better standardization has been afforded by crystalline derivatives. Variations in rapidity of action and excretion have been achieved, and the preparations developed for intravenous administration have proved most useful when rapid digitalization is desired. However, in spite of these newer developments, opinions concerning the most satisfactory digitalis preparation are widely divergent. In general, familiarity with the drug used and its judicious administration have appeared more important in most cases than the actual product used. It is probably true that a well-standardized digitalis leaf preparation is as efficacious as any of the purified products in the treatment of the average case of cardiac decompensation.

Recently the studies of Batterman and associates [1] have initiated a revival of the use of gitalin, a water-soluble amorphous mixture of glycosides first isolated from Digitalis purpurea by Kraft [2] in 1912. On the basis of clinical studies, they again established the efficacy of gitalin in the digitalization and maintenance of patients in cardiac decompensation. They felt that toxicity is less likely with gitalin than with other preparations and concluded that it is the digitalis agent of choice in treatment of patients with congestive failure.

Gitalin was marketed for clinical use a number of years ago abroad and in this country under the name verodigen.® The Germans [3] believed its absorption and excretion were optimal to achieve and maintain good therapeutic effect and considered it to be superior to the other digitalis preparations.

The American investigators in the 1930's did not stress this superiority. Stroud and associates [4] showed by biological assay that the preparation was about 130 times

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1. Batterman, R. C.; DeGraff, A. C.; Gutner, L. B.; Rose, O. A., and Lhowe, J.: Studies with Gitalin (Amorphous) for the Treatment of Patients with Congestive Heart Failure, Am. Heart J. **42**:292 (Aug.) 1951.

2. Kraft, F.: Die Glykoside der Blatter der Digitalis purpurea, Arch. Pharmacie **250**:118, 1912.

3. Straub, W., and Krehl, L.: Über Verodigen (Gitalin), Deutsche med. Wchnschr. **45**:281 (March 13) 1919. Mansfeld, G., and Horn, Z.: Untersuchungen über die Wirkungsweise des Gitalins, Arch. exper. Path. u. Pharmakol. **144**:46, 1929.

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more potent than dry standardized leaf but found the clinical potency in human beings to be considerably greater, 360 to 1. They demonstrated that the preparation did not deteriorate with age and with it were able to reproduce the clinical and electrocardiographic effects of digitalis leaf. Baker and Bloom [5] used verodigen* in patients and confirmed its clinical effectiveness. They felt that it was very well borne by the gastrointestinal tract, having noted no gastric disturbances on moderate overdosage. Levy and Boas [6] in a study on 36 patients with atrial fibrillation concluded that 0.8 mg. of gitalin was equivalent clinically to 0.2 gm. of digitalis leaf. In their patients its action seemed closely to parallel that of digitalis leaf.

PRESENT STUDY

In the past year we have made a study on use of gitalin in the management of 135 patients with cardiac decompensation at the University of Texas School of Medicine. Forty-two were hospital patients, and the remainder were ambulatory patients treated in the outpatient clinic. The duration of follow-up observations with gitalin therapy varied from 2 to 12 months. The patients in general were an unselected group and formed a representitive cross section of adults

TABLE 1.—*Data on Clinical Material (135 Cases)*

Type of Cardiovascular Disease*	Cases
A.S.H.D.	50
H.C.V.D.	22
A.S.H.D. and H.C.V.D.	37
Rheumatic	9
Syphilitic	10
Cor pulmonale	5
Congenital	1
Myocarditis	1

Rhythm	Cases
Sinoatrial, regular	98
Atrial fibrillation	34
Atrial flutter	1
Sinus rhythm with 2:1 block	1
Complete heart block	1

Age, Yr.	Cases
10-19	2
20-29	2
30-39	8
40-49	18
50-59	29
60-69	42
70-79	25
80-89	8
90-99	1

Sex	Cases
Male	81
Female	54

Race	Cases
White	72
Negro	63

* A.S.H.D. is arteriosclerotic heart disease, and H.C.V.D. is hypertensive cardiovascular disease.

with cardiac decompensation being seen at present. All factors which tended to interfere with the study of the drug, such as use of diuretics, were avoided whenever possible or, if avoidance was not possible, were kept the same as before the beginning of the clinical trial. The out-clinic patients were closely followed at daily and two-day intervals during digitalization, at intervals of twice weekly thereafter, and, when the maintenance dosage was established, at intervals of one to four weeks. The distribution of clinical material according to type of cardiovascular disease, rhythm, sex, race, and age is shown in Table 1.

INITIAL DIGITALIZATION

Most of the patients who were initially digitalized with gitalin had never had digitalis before. No patient is included in this group who had received any type of digitalis preparation for at least four weeks previous to gitalin administration. The method of digitalization was generally the one recommended by Batterman and colleagues,[1] consisted of 2.5 mg. as the initial dose and 1.5 mg. each six hours until a therapeutic response was obtained. In some cases effective dose modifications were

5. Baker, J. P., Jr., and Bloom, N.: Clinical Studies on Verodigen, a Digitalis Glucoside, Ann. Int. Med. **10**:605 (Nov.) 1936.

6. Levy, H., and Boas, E. P.: Clinical Studies of Gitalin and of Digitalis in the Treatment of Auricular Fibrillation, Am. Heart J. **15**:643 (June) 1938.

substituted. In several, 1.5 mg. was given three times daily until digitalization was attained. In others, 2.5 mg. was given twice at six-hour intervals, and then smaller doses of 1.0 mg. each six hours. In two cases 3.0 mg. was given initially, with smaller doses of 1.5 and 1.0 mg. each six hours. Satisfactory digitalization in a slower manner was produced in several patients by giving 0.5 mg. four times daily for three or four days until a therapeutic response was obtained. Whenever possible, hospital patients had a preliminary period of bed rest for several days, and use of mercurials was avoided during the digitalization period.

In this manner 49 patients were digitalized orally with gitalin, 21 of which were hospital patients. Both hospital and ambulatory patients were closely followed during the administration to determine the minimal point of therapeutic response.

TABLE 2.—*Total Gitalin Dosage for Full Digitalization (44 Patients)*

Dose, Mg.	No. of Patients	Dose, Mg.	No. of Patients
4.5	2	7.5	3
5.5	3	8.0	6
6.0	4	8.5	1
6.5	5	9.0	1
7.0	19		

TABLE 3.—*Atrial Fibrillation Treated with Gitalin*

Patient	Sex	Age	Diagnosis	Initial Rate	Dosage in 2 Days, Mg.	Final Ventricular Rate	Maintenance Dose, Mg./Day
J. B.	M	67	A.S.H.D.	165	8.0	80	1.0
H. D.	M	69	A.S.H.D. and H.C.V.D.	170	8.0	88	1.0
G. C.	M	62	A.S.H.D.	132	4.5	80	0.5 and 1.0 alternating
O. G.	F	67	H.C.V.D.	115	8.5	84	1.0 and 1.5 alternating
W. R.	M	68	A.S.H.D.	128	7.0	68	0.5
H. M.	M	56	A.S.H.D. and H.C.V.D.	154	5.5	85	1.0
C. A.	M	65	Syphilitic cardiovascular disease	143	7.0	68	0.5
E. W.	F	16	Rheumatic heart disease	164	8.0	76	0.5 and 1.0 alternating

Table 2 summarizes the total amounts of gitalin required for full digitalization in 44 patients. Although most patients were digitalized in 48 hours, for all patients requiring more than this period for full digitalization 0.5 mg. was subtracted as an excretion factor for each day over the 48-hour period.

Digitalization was generally accomplished with ease and was manifested by clearing of the symptoms and signs of cardiac decompensation. There was considerable variance in the digitalizing dose, from a minimum of 4.5 mg. to a maximum of 9.0 mg., but a large proportion of the patients was adequately digitalized with 7.0 mg. of gitalin. The average digitalizing dose for this group was 6.5 mg.

Adequacy of digitalization can be determined with greatest precision in the patients having cardiac decompensation with atrial fibrillation. Unless there is a preexisting block in auriculoventricular conduction, the ventricular rate in such instances serves as an adequate guide and should be reduced to 65 to 80 per minute. Gitalin was administered to eight undigitalized patients with atrial fibrillation, and detailed results of initial digitalization and maintenance are summarized in Table 3.

Four patients not included in Table 2 were unintentionally overdigitalized, because toxic effects appeared before the therapeutic level was recognized. Three of these received 7.0 mg. of gitalin in 48 hours, one presenting nausea and vomiting, another nausea and diarrhea, and a third bigeminy as evidences of toxicity. Another patient received 8.0 mg. of gitalin in a similar period and then exhibited nausea and diarrhea. For one patient, a 49-year-old white man with chronic cor pulmonale due to lung cysts and in congestive failure, the digitalizing order was misinterpreted, and the patient received 2.5 mg. each eight hours for a total of 35.0 mg. in four and one-half days. However, in spite of this high dosage, no toxic symptoms or signs occurred, and he was thereafter maintained on 1.0 mg. of gitalin per day.

MAINTENANCE THERAPY

The maintenance dose of gitalin was found to be easily established in nearly all the patients studied. As the tablets furnished each contained 0.5 mg., it was found desirable to give the preparation in multiples of these tablets. Thus, frequently the amount administered per day varied, with alternating doses being given.

TABLE 4.—*Maintenance Schedules*

Dosage, Mg.	No. of Cases		
	Not Adequate	Adequate	Toxic
0.5 every other day	..	3	..
0.5, skip each 3d day	..	4	..
0.5 daily	23	82	8
0.5 and 1.0/day alternating	10	20	8
1.0 daily	3	18	10
1.0 and 1.5/day alternating	..	3	..
1.5 daily	..	1	2
2.0 daily	..	..	1
Total	36	131	29

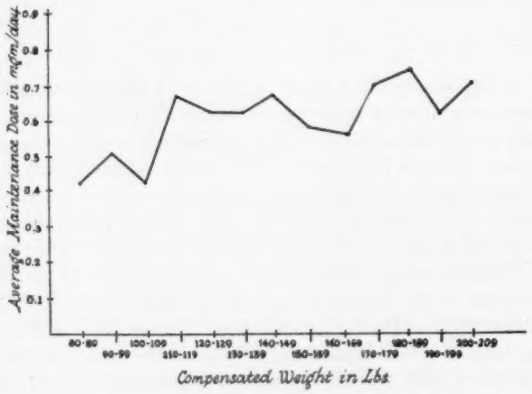
A summary of the maintenance doses found to be inadequate, adequate, and toxic for 131 patients who were followed for longer than two months is given in Table 4. An adequate maintenance dose was determined, usually with ease, for all patients except two. One of these was a 77-year-old white woman with arteriosclerotic heart disease, previously maintained satisfactorily with 0.1 gm. of digitalis leaf per day. Transferral of this patient to 0.5 mg. of gitalin daily resulted in nausea and vomiting after one week, and she resumed taking digitalis leaf as before at her own insistence. Another patient, a 36-year-old man with syphilitic and hypertensive cardiovascular disease, showed acute left ventricular failure after penicillin therapy, presumably on the basis of a Herxheimer reaction. Digitalis leaf in doses of 0.1 gm. per day produced bigeminy, which persisted with administration of 0.5 mg. of gitalin per day. All treatment with digitalis preparations was discontinued, and signs of decompensation disappeared with bed rest.

Eighty-two patients were satisfactorily maintained with doses of 0.5 mg. of gitalin daily, while the majority of the remainder had to be given larger amounts. Only very few had to be given more than 1.0 mg. per day to bring about compensation. Our method usually was to stop increasing the dosage when an adequate therapeutic amount was established. For a few of the patients who could be followed very closely, the doses were deliberately increased to determine the minimum toxic levels and the evidences of toxicity.

In order to determine the dose of gitalin which would correspond to various maintenance doses of other digitalizing agents, 68 patients considered satisfactorily treated with digitalis leaf or digitoxin were transferred to gitalin therapy. Equivalence of effects in such a study can be determined particularly well in patients with

TABLE 5.—*Well-Maintained Patients Transferred to Adequate Doses of Gitalin*

Gitalin Dosage Digitalis Leaf	No. of Cases	0.5 Mg. Every Other Day	0.5 Mg., Skip Every 3d Day	0.5 Mg. Daily	0.5 & 1.0 Mg. Alternating	1.0 Mg. Daily	1.0 & 1.5 Mg. Alternating
Maintenance, 0.1 gm./day							
Atrial fibrillation	16	1	1	11	1	1	1
Sinus rhythm	40	..	1	25	8	6	..
Sinus with 2:1 AV block	1	..	..	1	..	..	..
Maintenance, 0.1 gm. every other day							
Atrial fibrillation	1	..	..	1	..	..	..
Maintenance, 0.1 gm., skip each 3d day							
Atrial fibrillation	3	1	1	1	..	..	..
Maintenance, 0.1 and 0.2 gm. alternating							
Atrial fibrillation	1	..	..	..	..	..	1
Digitoxin							
Maintenance, 0.1 mg./day							
Sinus rhythm	3	..	..	3	..	..	..
Maintenance, 0.1 and 0.2 mg. alternating							
Sinus rhythm	1	..	..	1	..	..	..
Maintenance, 0.2 mg.							
Sinus rhythm	2	..	..	..	2	..	..



Relation of gitalin dosage to body weight.

atrial fibrillation, for the ventricular rate can be used as an index of digitalization. Table 5 summarizes these results and shows that there is no constant equivalence from patient to patient. However, the majority of patients receiving 0.1 gm. of digitalis leaf per day can be satisfactorily maintained on 0.5 mg. of gitalin per day, and only rarely is this dose toxic. A few patients require increased amounts of gitalin, such as alternating doses of 0.5 and 1.0 mg. per day or 1.0 mg. per day.

In general, the higher the maintenance dose of digitalis leaf or digitoxin, the higher is the gitalin requirement.

There is a rough correlation between the size of the digitalizing and maintenance dose of gitalin and the weight of the patient. The graph demonstrates that the average maintenance dose of gitalin tends to rise with the increase in compensated weight of the patient. This variation of dosage with weight has been noted with all digitalis preparations and is particularly important in children. However, other factors, such as absorption, size of the heart chambers, and degree of cardiac reserve, are also operative. Thus, no uniform rule of weight can be applied which is valid for each individual case.

TOXIC EFFECTS

Most of our instances of toxicity were avoidable and were attained by deliberate increase in dosage after the minimal therapeutic level was known to have been reached. Four patients were inadvertently pushed to toxic levels during initial digitalization with gitalin, as noted previously. Table 6 lists the minimal maintenance dose for therapeutic effect and the corresponding minimal dose for toxic effects in

TABLE 6.—*Minimal Therapeutic and Toxic Maintenance Doses of Gitalin (22 Cases)*

Minimal Therapeutic Dosage, Mg./Day	No. Patients	Minimal Toxic Dosage, Mg./Day			
		0.5	0.75	1.0	1.5
0.25	2	2	..	..	..
0.33	2	2	..	..	..
0.37	1	1	..	..	..
0.5	10	..	4	4	2
0.75	5	..	..	5	..
0.86	1	..	..	1	..
1.0	..	..	..	..	1

22 patients. In the preparation of this table, if varying daily doses were used, the average quantity per day was listed. In six of these patients, the toxic effects were obtained inadvertently on transfer to what was considered an equivalent gitalin dosage, but in the remainder the dosage was deliberately increased to toxic levels. The average minimal maintenance dose of gitalin in this group was 0.54 mg., and the average minimal toxic dose was 0.91 mg. Thus, the maintenance dose is 59.5% of the toxic dose, a figure somewhat higher than the ratio of 41% reported by Batterman and associates.[1]

Four patients not included in Table 6 displayed toxic effects because of failure to take the drug as instructed. Two took 0.5 mg. of gitalin three times daily instead of once daily. Another patient, a 46-year-old hypertensive Negro woman with atrial fibrillation, diregarded directions and took 2.0 mg. daily as a maintenance dose. After two weeks she had runs of multifocal ventricular premature beats but no toxic symptoms except weakness. Another patient, a 39-year-old white man with lower nephron nephrosis and uremia, showed signs of hypopotassemia on the electrocardiogram and had an episode of paroxysmal ventricular tachycardia while receiving a gitalin maintenance dosage of 0.5 mg. per day. The arrhythmia was reverted to sinus rhythm with intravenous administration of procaine amide. He had no further episodes with the same maintenance dosage after the hypopotassemia was corrected.

The symptoms and signs of gitalin toxicity in 30 patients are summarized in Table 7 and appear similar in type to those of toxicity to other digitalis preparations.[7] It would be desirable to have symptoms appear prior to, or at least simultaneously with, disturbances of cardiac mechanism, as they draw attention to the condition. Also, vomiting, if present, tends to act as a safety valve to prevent further accumulation of the drug. Abnormalities of cardiac mechanism appeared in 18 of the patients, but in 8 of these symptoms of toxicity appeared at the same time. Symptoms without toxic signs were present in 12 patients. The appearance of ventricular tachycardia and of runs of multifocal ventricular premature beats were regarded as particularly serious because of the possibilities of ventricular fibrillation and death. However, no fatalities which could be ascribed to gitalin were encountered in this series.

TABLE 7.—*Symptoms and Signs of Gitalin Toxicity (Thirty Cases)*

Symptoms Only	Cases	Signs Only	Cases
Nausea and diarrhea	2	Bigeminy	5
Anorexia and nausea	3	Complete AV block	1
Anorexia, nausea, and vomiting	5	Wenckebach AV block	1
Xanthopsia, nausea, and vomiting	2	Atrial fibrillation with very slow ventricular rate	2
Total	12	Total	9
Symptoms with Signs		**Signs with Symptoms**	
Weakness and anorexia	4	Bigeminy	3
Anorexia and nausea	1	Multifocal ventricular premature beats	1
Anorexia, nausea, and vomiting	3	Paroxysmal ventricular tachycardia	1
Total	8	Nodal tachycardia	1
		Atrial fibrillation with very slow ventricular rate	2
		Total	8
Symptoms After Signs		**Signs Before Symptoms**	
Xanthopsia, nausea, and vomiting	1	Frequent premature beats	1

REFRACTORY CASES

There are two drug levels of significance in the management with digitalis derivatives of the patient having cardiac decompensation. One of these is the minimal dosage for adequate therapeutic effect, and the other is the lowest level at which toxic signs or symptoms appear. The difference represents the therapeutic range, at any point of which the therapeutic effect is satisfactory but within which there are no evidences of toxicity. In the patient with fair cardiac efficiency, these levels are considerably different, and thus digitalization can be accomplished with ease, regardless of the preparation administered. However, as the cardiac reserve diminishes, the margin of safety or the difference between the minimal therapeutic and the toxic dose becomes less. Finally, the stage may be reached at which the patient with most serious myocardial damage becomes toxic before therapeutic effects can be attained, in spite of all the adjunct therapies for controlling cardiac decompensation.

Batterman and associates [1] reported that in their series the therapeutic ratio of gitalin was only 41%, whereas the therapeutic ratio for digoxin, digitoxin, and lanatoside C had been previously found to be 63.6, 65.4, and 62.9% respectively.[8] Thus, they concluded that gitalin is the drug of choice in cardiac decompensation.

7. Herrmann, G. R.; Decherd, G. M., Jr., and McKinley, W. F.: Digitalis Poisoning, J. A. M. A. **126**:760 (Nov. 18) 1944.

8. Batterman, R. C., and DeGraff, A. C.: Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C, for the Management of Ambulatory Patients with Congestive Heart Failure, Am. Heart J. **34**:663 (Nov.) 1947.

TABLE 8.—*Patients with Refractory Failure Improved with Gitalin Therapy*

Patient	Age	Cardiovascular Type Disease	Rhythm	Previous Medication and Results	Gitalin Dosage Required, Mg./Day	Results
H. G.	31	Rheumatic mitral stenosis	Atrial fibrillation	Persistent failure on all dosage schedules, digitalis leaf; bigeminy and nausea on 0.1 gm./day	0.5 and 1.0 alternating	Compensated; no toxicity
N. P.	43	H. C. V. D.	Sinus	Digitalis leaf 0.1 gm./day, continued failure; 0.1 and 0.2 gm./day, nausea and congestive failure	0.5	Much improved; no nausea
E. P.	78	A. S. H. D.	Sinus	Digitoxin 0.1 mg./day, decompensation; 0.1 and 0.2 mg./day alternating, nausea and vomiting	0.5 and 1.0 alternating	Decompensation improved; toxicity disappeared
M. P.	57	H. C. V. D.	Atrial fibrillation	Digitalis leaf 0.1 gm./day, decreased ventricular rate to 74, but still left ventricular failure	0.5	Ventricular rate same, but left failure disappeared
V. M. P.	65	A. S. H. D.	Atrial fibrillation	Digoxin 0.5 mg./day, ventricular rate to 75, but failure, with nausea and vomiting	0.5	General condition better; toxicity disappeared; ventricular rate same
P. W.	50	H. C. V. D.	Sinus	Digitalis leaf 0.1 gm./day, continued decompensation and bigeminy; decreased dosage, failure continued	0.5 and 1.0 alternating	Decompensation improved; bigeminy disappeared
P. L. W.	78	A. S. H. D.	Atrial fibrillation	Digitalis leaf 0.1 gm./day, ventricular rate, 70, still left failure; if increased, nausea and vomiting	0.5	Ventricular rate 70; much better
J. B. S.	48	A. S. H. D.	Sinus	Digitalis leaf 0.1 gm./day, refractory failure; nausea and vomiting on increased dosage	1.0	No toxicity; failure continued but less severe

Since this greater margin of safety would appear of particular importance for patients with marked cardiac damage, we were interested in the evaluation of gitalin for patients in apparently refractory failure. Thus, we chose 18 patients who remained in chronic congestive failure despite shifting of the digitalis dosage to the point of toxicity, sodium restriction and frequent use of mercurials, xanthine derivatives, and acidifying diuretics, and in whom no electrolyte disturbance could be demonstrated.

Fifteen of these patients showed definite improvement with gitalin administration, but the dosage had to be carefully adjusted. However, review of the cases showed that in six the dosage of the prior digitalis preparation may not have been adequately regulated, there being a possibility of overdosage in four and of underdosage in two. Thus, the evidence of improvement was clear-cut in 15, and it seemed to be definitely related to gitalin administration in 9. Data on eight of these nine patients are summarized in Table 8. The remaining three patients did no better with gitalin than with other digitalis preparations.

COMMENT

The results of this study demonstrate that gitalin is an effective preparation for initial digitalization and maintenance of the patient in cardiac decompensation. Initial digitalization is generally easily accomplished, with divided oral doses, in 48 hours. The average digitalizing dose in this series was 6.5 mg., somewhat higher than the 5.9 mg. observed by Batterman and associates.[1] Most patients can be satisfactorily maintained with 0.5 mg. per day, but a substantial minority require larger doses, and a very few, smaller doses. Toxic effects are uncommon in routine management, and in one case 35 mg. was given in four and a half days without toxicity. The toxic signs and symptoms appear similar in type to those observed on overdosage of other digitalis preparations. Electrocardiographic effects also appear the same.

We were unable to duplicate the low therapeutic index found by Batterman and co-workers,[1] as our value of 59.5% obtained on the basis of maintenance doses is considerably higher than their reported value of 41%. However, the degree of cardiac damage may vary from series to series, as well as the criteria for minimal digitalization. The only truly comparable data for digitalis preparations would be those obtained on an identical series by the same observers—preferably with the same patients in each series. We did not do studies of minimal therapeutic and toxic doses using other digitalis preparations.

No definite studies on excretion were done, but it is our opinion that gitalin is excreted more rapidly than digitalis leaf and digitoxin, but slower than digoxin and lanatoside C. It may be that this excretion is the best one for proper maintenance, as suggested by the German authors, and that therein lies the apparent superiority of gitalin.

Gitalin appears particularly applicable as the agent of digitalis therapy in cases of congestive failure which is no longer responding to the ordinary treatment methods. It produced definite improvement in the majority of our selected group of patients in refractory failure, even though all other medications were unchanged. This would tend to lend support to Batterman's contention that toxic effects appear later with gitalin. It is in this group that gitalin appears to offer a real advantage over the other digitalis preparations.

SUMMARY

Gitalin was used in the initial digitalization of 49 patients with cardiac decompensation, and the maintenance dosage was determined for 131 patients. Forty-two of the patients were hospitalized.

The efficacy of gitalin in the digitalization and maintenance of patients in congestive failure is demonstrated. The average digitalizing dose was 6.5 mg., but varied from 4.5 to 9.0 mg.

The majority of patients were adequately maintained with 0.5 mg. per day, but a few required higher doses, and a very few, smaller doses. Equivalent doses of powdered digitalis leaf and digitoxin were shown to vary from patient to patient.

Toxic effects generally resulted from deliberate increase in dosage and were similar in type to those noted from other preparations. In 22 patients, the average minimal maintenance dose was 0.54 mg., and the average minimal toxic dose, 0.91 mg.

Improvement was noted in 15 of 18 patients with apparently refractory cardiac decompensation when treated with gitalin instead of with other digitalis preparations. In nine of these improvement seemed definitely related to the change to gitalin, but the dosage had to be carefully adjusted.

It is in the management of such apparently refractory cases that gitalin appears to offer a real advantage over the other digitalis preparations.

TENDENCY TOWARD HYPOTENSION IN LEFT LATERAL RECUMBENCY

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WITH THE aim of achieving a better insight into the pathogenesis of the cardiovascular accidents which still occur so frequently during surgical operations and often remain unexplained even on autopsy I observed, in 1949, a series of patients during thoracic surgical procedures.[1] Among the causes of cardiovascular complications noted, there was a shock-like state which in certain patients recurred several times when renewed attempts were made on different days to perform the intended operation or when different stages of a thoracoplasty were performed. Immediately or soon after the patient was turned to the lateral recumbent position, a pronounced fall in blood pressure was registered, and sometimes no blood-pressure readings could be obtained for certain periods. Yet, whenever the patient was returned to the supine or sitting position, the normal preoperative pressure readings were obtained immediately or a few minutes later (see Fig. 1). This positional complication occurred before the start of anesthetization, as well as during anesthetization; with local anesthesia and nerve block, as well as with general anesthesia. The tendency to hypotension apparently prevailed more frequently in the left than in the right lateral recumbency.

The importance of this phenomenon has since been acknowledged by several thoracic surgeons. But there is evidence that its importance goes far beyond its surgical aspects. Subsequent studies on a great number of nonsurgical patients confirmed the presence in many of a physiological mechanism with pathophysiological implications which, in a preliminary way, may be called "left lateral hypotension."

PRESENT STUDY

The present report concerns the results of a study on 100 unselected persons in whom the influence of various positions upon the arterial blood pressure was observed. The tests were performed in the sitting, supine, left lateral, and right lateral positions. The sequence of these positions was changed from subject to subject. The rest periods after each turn from one position into another were kept equal in duration. For confirmation of the pressure readings, the tests were repeated for some of the subjects, and some repeat examinations were performed after exercise.

The statistical results which are submitted in Tables 1, 2, and 3 reveal that the great majority of the 100 subjects had their lowest arterial blood pressure in the left lateral position. It is

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This paper is based on a display presented at the Scientific Exhibit of the Twenty-Fourth Graduate Fortnight of The New York Academy of Medicine, October, 1951.

1. Stein, P., and Buchberg, A. S.: Arch. mal. coeur **44**:417, 1951. Gross, H.; Stein, P., and Buchberg, A. S.: Anesth. & Analg. **30**:250 and 314, 1951.

noteworthy that in certain persons a small difference in the degree of the body's rotation to the left side may significantly influence the level of the blood pressure.

Though unselected, 81% of these subjects had some degree of cardiovascular disease. This was due to the fact that only patients attending the cardiac clinics of either City Hospital or Gouverneur Hospital, in New York City, and a few of my private patients were included in the statistics. The subjects observed during operations were patients of Montefiore Hospital; they are not included in the statistical material. However, for 13% of the subjects the diagnosis was "normal" and for 6% the diagnosis was deferred as "uncertain."

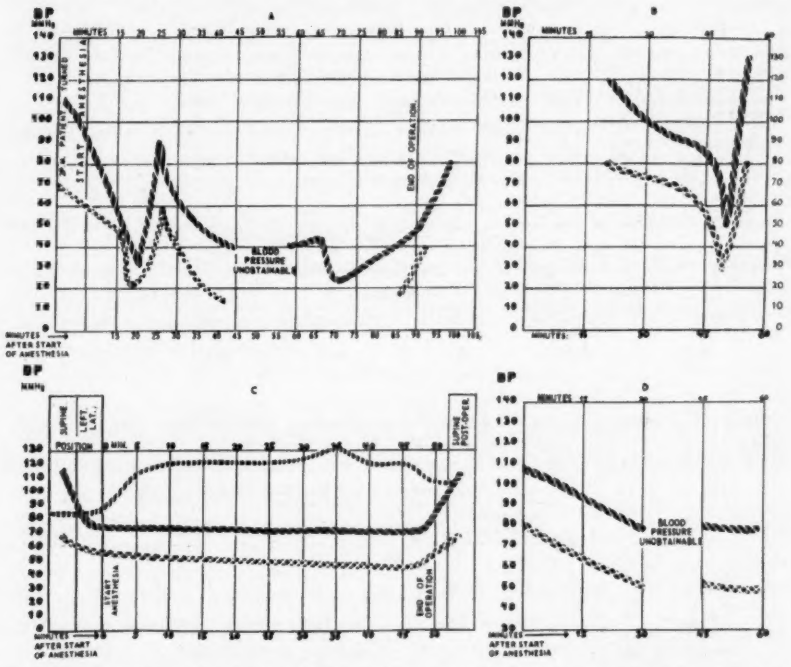

Fig. 1.—Left lateral hypotension preventing or complicating thoracic surgery. Patient M. K., a 40-year-old woman, had pulmonary tuberculosis. On four occasions, before as well as during anesthesia and surgical procedures, blood pressure fell when patient was turned on her left side. On graphs lower line represents diastolic pressure, and upper line, systolic pressure, except on Graph *C* in which lowest line represents diastolic pressure, middle line, pulse rate, and upper line, systolic pressure.

Graph *A* demonstrates the immediate drop in blood pressure after patient was turned on her left side. Anesthetization was begun about seven minutes later. For about 15 minutes no blood-pressure reading could be obtained. Surgical procedure was abandoned after division of superficial muscles.

At a second attempt (Graph *B*) patient was under anesthesia induced with cyclopropane, which she received while in supine position. About 20 minutes after induction of anesthesia she was turned on her left side. At this point blood pressure began to fall continuously, and operation was canceled. Rapid rise of pressure curves as seen in Graph *B* occurred after patient had been returned to supine position.

At third surgical attempt (Graph *C*) first stage of thoracoplasty could be performed. Throughout operation patient appeared to be in poor condition. Drop in blood pressure which occurred five minutes before start of anesthetization (local anesthesia and nerve block) and immediate rise of pressure to its preoperative level when patient was returned to supine position are shown in Graph *C*.

During second stage of thoracoplasty (Graph *D*), almost identical conditions prevailed. For some time no blood-pressure readings could be obtained.

RESULTS

All individual readings of the systolic and diastolic pressures were computed for each of the four positions in all the 100 subjects. Table 1 reveals that the average systolic pressure was found to be 22.93, 22.16, and 22.35 mm. lower in the left lateral than in the sitting, supine, and right lateral positions, respectively. The average

TABLE 1.—*Computed Total and Average per Patient of One Hundred Blood-Pressure Readings*

Position	Sitting		Supine		Right Lateral		Left Lateral	
Blood Pressure, Mm. Hg	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Total in 100 patients.....	15,019	9,028	14,942	8,754	14,961	9,300	12,726	7,287
Compared with total in left lateral position....	+2,293	+1,741	+2,216	+1,467	+2,235	+2,013	.....	.....
Average blood pressure per patient	150.19	90.28	149.42	87.54	149.61	93.00	127.26	72.87
Compared with average in left lateral position.	+22.93	+17.41	+22.16	+14.67	+22.35	+20.13	.....	.....

TABLE 2.—*Total Blood Pressure in Left Lateral Position As Percentage of Blood Pressure in Sitting, Supine, and Right Lateral Positions*

Sitting		Supine		Right Lateral	
Systolic, %	Diastolic, %	Systolic, %	Diastolic, %	Systolic, %	Diastolic, %
84.73	80.71	85.16	83.24	85.06	78.35

TABLE 3.—*Patients with Lowest Blood-Pressure Readings with Reference to Left Lateral Position and Distribution of Readings*

	Blood Pressure in Left Lateral Position							
	Lowest Systolic and Diastolic		Lowest Systolic		Lowest Diastolic		Neither Systolic Nor Diastolic	
	No.	%	No.	%	No.	%	No.	%
Group I* Total, 61	41	67.21	8	13.11	9	14.75	3	4.92
Group II† Total, 39	22	56.41	5	12.82	3	7.69	9	23.08
Distribution of 100 blood-pressure readings	63		13		12		12	

* Group of 61 patients who in supine position had blood-pressure readings of more than 140 mm. Hg systolic and/or more than 90 mm. Hg diastolic.

† Group of 39 patients who in supine position had blood-pressure readings of 140 mm. Hg or less systolic and/or 90 mm. Hg or less diastolic.

Sixty-three per cent of the tests revealed the lowest systolic as well as the lowest diastolic blood pressure in the left lateral position. Of the 12% of the patients with readings which revealed neither the lowest systolic nor the lowest diastolic blood pressure in the left lateral position, only 4.92% had a systolic pressure over 140 mm. or a diastolic pressure of over 90 mm. Hg.

differences per patient in the diastolic pressures were 17.41, 14.67, and 20.13 mm. respectively.

The computed total in millimeters of mercury for all systolic pressure readings in the left lateral position amounted to only 84.73% of the total in sitting, to 85.16% of the total in supine, and to 85.06% of the total in the right lateral position. For the diastolic pressure, the results were 80.71, 83.24, and 78.35%.

Another insight can be gained if the 100 subjects are divided in two groups, Group I comprising all patients in whom the systolic pressure in supine position was

higher than 140 mm. and/or the diastolic pressure higher than 90 mm., and Group II comprising all patients in whom the systolic pressure was 140 mm. or lower and the diastolic pressure was 90 mm. or lower. Table 3 shows that in Group I 41 patients (67.21%) had the lowest systolic pressure as well as the lowest diastolic reading in left lateral recumbency. Eight patients (13.11%) showed only the systolic and nine patients (14.75%) only the diastolic pressure to be lower in the left lateral than in any other position. Of all the 61 patients in this group, only 3 (4.92%) had neither systolic nor diastolic pressure lower in the left lateral than in any of the other positions.

A pronounced prevalence in the number of patients who have the lowest blood pressure in the left lateral position was also found in Group II, which comprised 39 patients. However, this prevalence is less impressive in the lower blood-pressure ranges which are represented in this group. Nevertheless, 56.41% of these persons showed their lowest systolic and diastolic pressure in the left lateral position, and not more than 23.08% had neither a lower systolic nor a lower diastolic pressure in left lateral recumbency than in any other position.

If all 100 subjects are considered, then it is seen that 63% of all subjects examined had their lowest systolic as well as diastolic pressure in the left lateral position. And only 12% showed neither systolic nor diastolic pressure to be lowest in the left lateral recumbency.

COMMENT

Evidently the degree of "left lateral hypotension" varies individually. But so many subjects, including healthy persons, have a lower arterial pressure in left lateral recumbency as compared with the other positions that one may rightly speak of a physiological phenomenon.

Not only the degree, but also the symptomatology, of left lateral hypotension varies. Some persons are entirely undisturbed by the drop in arterial pressure. They lie or even sleep on their left side as comfortably as on their right. Many persons "do not like" to lie on their left but prefer to sleep on their right side; many others tell of a more distinct but by no means serious discomfort, while others suffer pronounced distress in left lateral position. Some of the patients stated voluntarily, others admitted on questioning, their intolerance of the left lateral recumbency. In several instances patients complained of increasing distress, breathing difficulties, tightness, pressure, or even pain in the chest while they were held in left recumbency before or during the blood-pressure examinations. They felt well immediately and their blood pressure rose after they had turned to another position.

It appears from this experience that abnormal symptoms of major significance are produced by left lateral hypotension, particularly under certain pathological conditions, as those of the mediastinum and lungs, coronary insufficiency, reduced myocardial functional capacity, hypertensive disease, and, in many persons, abnormal position and abnormal mobility of the heart.

In these persons who suffer when lying on their left side, the fall in blood pressure may be the cause of their symptoms, or it may be a correlated sign produced by another underlying cause. It is surprising that the phenomenon of left lateral hypotension which so frequently occurs has not only remained unnoticed in medical

literature, but that even the fact, known widely, that many persons suffer severely in this position has failed to initiate thorough investigation. The lack of explorative work in this direction is all the more surprising since Wood and Wolferth in 1937 called attention to left lateral intolerance in many patients with heart disease. They observed that many persons with cardiac disease are unable to tolerate one certain position, "usually the left lateral." Cough, anginal pain, and dyspnea were noted by these investigators to be the most frequent symptoms appearing when the critical

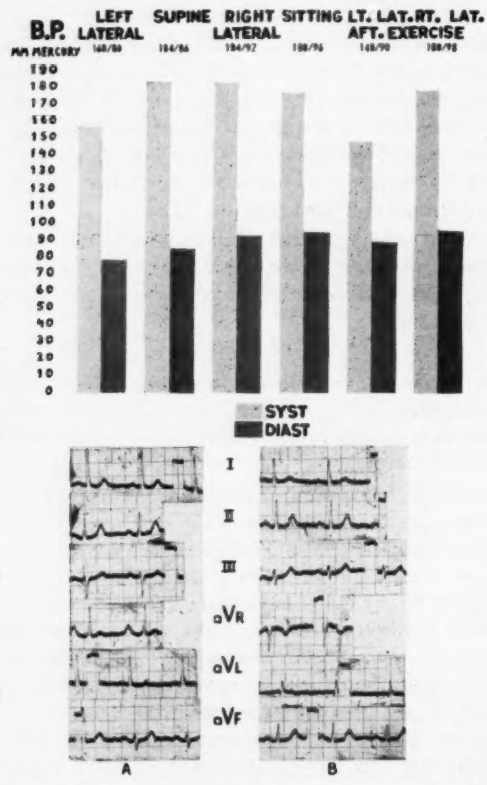

Fig. 2.—Sample case. Upper part shows blood-pressure readings in various positions, with a two-minute rest before each test. Lower part shows standard and unipolar limb leads on electrocardiograms made in supine position (*A*) and in left lateral position (*B*). In left lateral position electrocardiogram shows signs of clockwise rotation.

Patient C. R., a woman 68 years old, had hypertensive arteriosclerotic cardiovascular disease, with the main complaint of moderate chest pain when lying on left side. She was Patient 11037 at Gouverneur Hospital Cardiac Clinic.

position is assumed.[2] Scherf called my attention to a case report published by him in 1947. One of his patients, who presented no other cardiac abnormalities but a low T wave in the first standard lead of the electrocardiogram, complained that he

2. Wood, F. C., and Wolferth, C. C.: Am. J. M. Sc. **193**:354, 1937.

felt "terrible" and had anginal pain when lying on his left side. When, upon the urging of a nurse, he tried to remain in this position, he died.[3]

A fall in blood pressure on assuming the right lateral position seems to occur only rarely. One of the surgical patients observed suffered a fall in blood pressure to 40/15 mm. so that the operation had to be canceled. As soon as the patient was turned on her back, the pressure rose at once to 120/80 mm.

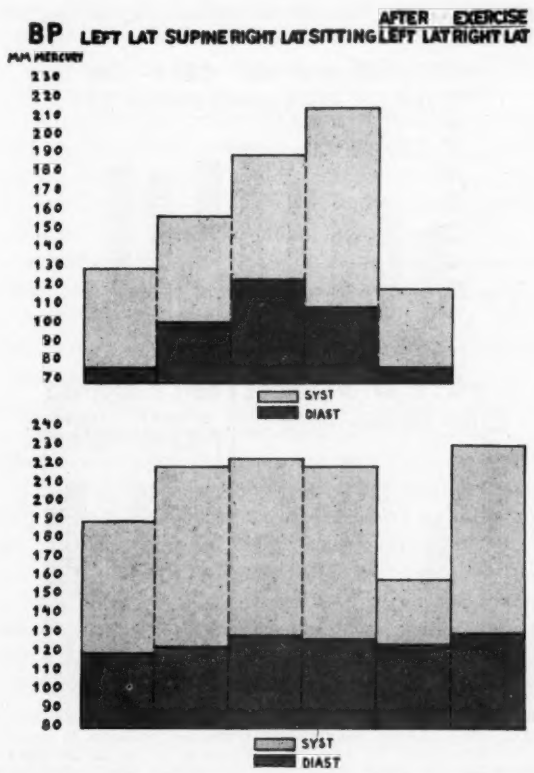

Fig. 3.—Two sample cases, showing blood-pressure readings in various positions and after exercise. Upper chart is for Patient J. J., a woman 70 years old, with essential hypertension, seen at City Hospital Dispensary. Her main complaint was chest pain on walking. Lower chart is for Patient I. M., a woman 63 years of age, seen at Gouverneur Hospital Cardiac Clinic, with hypertensive cardiovascular disease and coronary sclerosis. Her main complaint was angina pectoris, which was relieved by administration of glyceryl trinitrate (nitroglycerin). There was a one-minute rest between tests.

The exploration and interpretation of the phenomenon of left lateral hypotension and, in general, of left lateral intolerance, will have a number of theoretical starting points. Certain anatomical, physiological, pathological, and roentgenologic facts

3. Scherf, D., and Boyd, L. J.: Cardiovascular Diseases, Philadelphia, J. B. Lippincott Company, 1947, p. 248.

which have been more or less well established may be related to the phenomenon of left lateral hypotension and to its gravest exaggeration, which may be called "postural shock."

It has been known that the rotation of the body to a lateral position causes a shift of the heart toward the side to which the body is rotated, unless the mediastinum is fixed.[4] When the body is turned on its left side, the shift of the heart and its rotation around its long axis produce, in general, a tendency to right axis deviation in the electrocardiogram. Zdansky[5] described extensively the changes seen roentgeno-

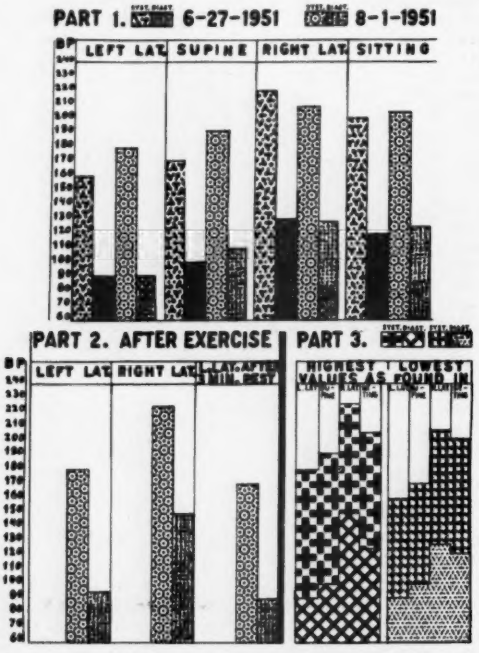

Fig. 4.—Sample case, with comparison of results of two examinations. Graphs show blood-pressure readings. Part 1 includes readings on two different occasions in various positions, with a 1-minute rest before each test. Part 2 shows readings in left lateral and right lateral positions after exercise, with the left lateral reading after a 3-minute rest. Part 3 shows highest and lowest blood-pressure values found in various positions. Patient C. V., a 56-year-old woman (City Hospital Dispensary, Patient No. 59902), had hypertensive cardiovascular disease. Her main complaints were chest pain on exertion, relieved by administration of glyceryl trinitrate, and inability to sleep on left side because of coughing. Patient sleeps on right side.

logically in the lateral positions: The mediastinum sinks toward the underlying hemithorax; due to the increase in intra-abdominal pressure on the side on which the patient rests, the diaphragm rises on this side. On the contralateral side the

4. Dieuaide, R. F.: Arch. Int. Med. **30**:362, 1928. Master, A. M.: Electrocardiogram and X-Ray Configuration of the Heart, Philadelphia, Lea & Febiger, 1946. Nathanson, M. H.: Proc. Soc. Exper. Biol. & Med. **28**:766, 1931.

5. Zdansky, E.: Roentgendiagnostik des Herzens und der grossen Gefaesse, Berlin, Springer-Verlag, 1949.

abdominal pressure is reduced; the diaphragm flattens and descends. More changes occur in left than in right lateral position on account of the greater mobility of the left side of the heart. Thus, to a greater extent left recumbency will lead to (*a*) shift, (*b*) clockwise rotation, and (*c*) elevation of the apex of the heart. As a result, while the concavity of the left upper border of the heart increases, more bulging and protrusion of the left ventricle into the lung field occur. Little change is observed at the right cardiac border. There, a slight flattening of the right auricular segment may be noticed. The more shifting of the heart occurs, the more transformation of the cardiovascular shadow is seen roentgenologically in the lateral positions.

The changes in the QRS and T axis which are seen after lateral rotation were found to be especially great in hypertrophic hearts. This was recently confirmed by Lepeschkin,[6] who refers to earlier reports by Jones, Hellerstein, and Feil.[7] But the expected right axis deviation may be missed when the weighty hypertrophic heart, on lateral left rotation, undergoes a marked increase in its transverse position, resulting in left axis deviation, while very little rotation around its longitudinal axis (making for right axis deviation) will occur.

It should be pointed out, however, that from the radiologist's view it is not the large, hypertrophic heart which in left lateral position shows the greatest transformation, but the small, thin-walled, poorly filled heart (Zdansky).

I have no evidence to prove that either clockwise rotation or increased verticalization, or any form or degree of roentgenologic transformation, of the heart is an indicator (and less so a measure) of the actual causative events which in left lateral position lead to postural hypotension and to distressing symptoms.

Various mechanisms of circulatory embarrassment could be visualized as the possible causes of positional hypotension and of cardiac distress. Wood and Wolferth, in discussing the problem of why many persons with cardiac disease suffer in a certain position, "usually the left lateral," thought of a possible obstruction at certain points of the vascular circulation. They seemed to believe that the most probable site of obstruction would be the pulmonary veins and the left auricle, structures through which the blood flow proceeds under low pressure. Enlarged hearts may certainly supply the force required for their compression when they move on rotation of the body to its left side. Besides, these structures may also be "kinked as they enter the pericardium by a twist of the heart." While this interpretation refers to large hearts, earlier observers [8] have reported that persons with an unusual mobility of their hearts in the mediastinum, especially formerly obese persons after rapid weight reduction, suffer dyspnea and precordial distress when lying on their left side.

Unfortunately, no comparative positional studies of the cardiac output have been performed except in one of Wood and Wolferth's cases. In this instance the output was found to be markedly lower in the left than in the right lateral position.

6. Lepeschkin, E.: Modern Electrocardiography, Baltimore, Williams & Wilkins Company, 1951.

7. Jones, A. M.; Hellerstein, H. K., and Feil, H.: Brit. Heart J. **11**:94, 1949.

8. Pick, A.: Wien. klin. Wchnschr. **2**:747, 1889. Rumpf, D.: Verhandl. Cong. inn. Med. **7**:13, 1888. Hoffmann, A.: Ibid. **16**:316, 1898. VanZant, C. B.: Denver M. Times **29**:139, 1909.

Among the causative mechanisms which may bear some relation to the phenomenon of left lateral hypotension, a twist of the heart's pedicle at its entrance into the pericardium would be a factor if certain conditions prevail. The pericardium itself may be affected by the movements of the heart: Vagovagal reflexes of the type known to produce fall in blood pressure and shock would more readily occur in diseased and hypersensitive hearts. The resulting hypotension, reducing the coronary circulation significantly, would then explain the frequent appearance of anginal pain and dyspnea in patients with confirmed or suspected coronary disease whenever they rest on their left side.

Other vagal reflexes will also have to be considered, especially reflexes produced by distention due to positional effects of an abdominal viscus, or by stimulation of the pressor-receptors in the aorta, pulmonary artery, and the carotid sinus. In addition, changes in the intrathoracic pressure, in the venous return, and in ventilatory and respiratory, as well as in neuroregulatory, factors and the element of vascular reactivity may play essential roles in creating a tendency to left lateral hypotension.

Various considerations, for instance, the fact that most persons respond to the left lateral recumbency with an immediate fall (more or less pronounced) in both systolic and diastolic blood pressure, make any interpretation difficult, if it is based on the assumption of a single cause. A restriction or obstruction of the circulation at any point would not immediately reduce the diastolic pressure. It appears that not one single causative factor, but rather a concatenation or combination of factors takes effect in the production of left lateral hypotension and its serious complications.

Case Reports

WERNER'S SYNDROME

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AND
EDWARD P. CAWLEY, M.D.
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ORIGINALLY believed to be an excessively rare heredofamilial disorder, Werner's syndrome has been recognized with increasing frequency in recent years. The syndrome is featured by the unique combination of physical immaturity, early senescence, premature cataracts, scleroderma-like skin changes, and a tendency toward development of diabetes mellitus.[1] This multiplicity of clinical manifestations makes Werner's syndrome of interest to physicians in various branches of medicine.[2]

The varied components of Werner's syndrome do not appear in an orderly sequence and not all cases exemplify the syndrome in its entirety.[3] Evidences of physical immaturity in Werner's syndrome are the short stature, slender, tapering extremities, and stocky trunk surmounted by a protuberant abdomen.[4] Underdevelopment of the genitalia, as well as menstrual disturbances and a low degree of fertility, occurs commonly as part of the syndrome.[5] Signs of premature senescence appear in the third or fourth decade.[4] These include dry, wrinkled skin, gray hair,[6] cataracts, a weak voice, osteoporosis, and arteriosclerosis. Scleroderma-like changes in the skin of the lower legs, the feet, and occasionally the forearms and hands impart a hidebound character to these areas. Callosities develop at pressure sites in the sclerodermatous patches, and these callosities are prone to ulcerate, producing lesions which are exceptionally refractory to treatment.[1] Calcium may be deposited in the sclerodermatous and ulcerated skin, giving rise to the condition known as calcinosis circumscripta. These abnormal calcium deposits are regarded as local

From the Department of Dermatology and Syphilology, University of Virginia Department of Medicine.

1. (*a*) Thannhauser, S. J.: Werner's Syndrome (Progeria of Adult) and Rothmund's Syndrome, Ann. Int. Med. **23**:559-626 (Oct.) 1945. (*b*) Oppenheimer, B. S., and Kugel, V. H.: Werner's Syndrome: Report of First Necropsy and of Findings in a New Case, Am. J. M. Sc. **202**:629-642 (Nov.) 1941. (*c*) Sheets, R. F.: Werner's Syndrome (Progeria of Adult), Am. Pract. & Digest Treat. **1**:390-393 (April) 1950.

2. Pomeranz, M. M.: Werner's Syndrome: Case Report, Radiology **51**:521-524 (Oct.) 1948. Brink, A. J., and Findlay, C. H.: Werner's Syndrome: Ulcerating Atrophodermia, Cataract and Premature Senility; Report of a Case, South African M. J. **24**:318-321 (April 29) 1950.

3. Thannhauser.[1a] Schott, J., and Dann, S.: Werner's Syndrome: A Report of 2 Cases, New England J. Med. **240**:641-644 (April 21) 1949.

4. Carleton, A.: Skin Disease and Cataract, Brit. J. Dermat. **55**:83-98 (April) 1943.

5. Block, B., and Stauffer, H.: Skin Diseases of Endocrine Origin, Arch. Dermat. & Syph. **19**:22-34 (Jan.) 1929.

6. Weidman, F. D.: Ageing of Skin, in Problems of Ageing, edited by E. V. Cowdry, Baltimore, Williams & Wilkins Company, 1942, pp. 391-410.

metabolic alterations, since there is no evidence of a systemic disturbance of calcium metabolism in Werner's syndrome. When diabetes mellitus occurs in Werner's syndrome, it is usually mild, paralleling the arteriosclerosis in severity.[1a]

ABSTRACTS OF CASES OF WERNER'S SYNDROME

An opportunity was recently afforded to observe and study two sisters with Werner's syndrome in the Dermatology Service of the University of Virginia Hos-

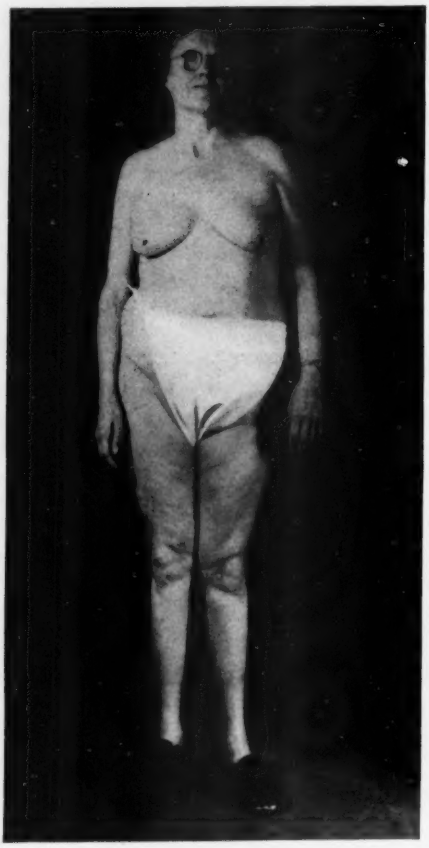

Fig. 1 (Case 1).—The stocky trunk and slender, tapering extremities are well illustrated.

pital. For a brother of these siblings the same diagnosis was made elsewhere, and his record has been made available to us. The first of the case abstracts (all three cases were practically identical in their clinical manifestations) is presented in some detail. The three patients described were siblings, and two of their grandparents were first cousins (Fig. 6).

CASE 1.—Mrs. O. A., a white housewife aged 49, noticed failing vision at the age of 35, and the following year a diagnosis of bilateral cataracts was made. Iridectomy was performed when the patient was 42 years old. At the age of 40 the patient's feet became painful and tender.

During the next three years scleroderma-like changes developed on the lower extremities, and an ulcer appeared over the left external malleolus. Calcification in the soft tissues of the feet and ankles was demonstrated by means of roentgenograms when the patient was 43 years of age.

The patient's past history was not remarkable otherwise. Menstruation began at the age of 14, and the menopause occurred at the age of 47. A single pregnancy terminated in miscarriage at two months.

The diagnosis of Werner's syndrome was made in 1951, when the patient was 49 years of age. Physical examination at that time revealed a short woman (height, 59 in. [150 cm.]) who weighed 107 lb. (48.5 kg.). The extremities were slender in comparison with the relatively stocky trunk, and the gait was halting because of painful, immobile feet. The face had a "bird-

Fig. 2 (Case 1).—Anterior view of lower legs.

like" appearance as the result of loss of subcutaneous fat, and the skin was generally dry and wrinkled. The scalp, axillary, and pubic hair was sparse and gray; the eyelashes were scant, and the eyebrows were practically absent. The toenails and fingernails showed increased longitudinal ridging. The skin of the distal half of each lower leg was atrophic, glossy, yellowish-brown, and remarkably hidebound. Scattered telangiectatic vessels traversed this skin. A large ulcer was present over the left Achilles tendon, and a fragment of calcareous material could be made out in the floor of another ulcer which was present over the left internal malleolus. The scar resulting from a previous ulcer was seen near the right external malleolus. The eyes showed typical postiridectomy changes. The larynx was within normal limits. Peripheral vessels showed no gross changes.

Laboratory findings in 1951, when the patient was 49 years of age, were as follows: Urinalysis showed no abnormality. The complete blood count and the spinal fluid were normal.

Blood urea measured 34 mg.; blood chlorides, 615 mg.; serum sodium, 350 mg.; cholesterol, 207 mg.; serum calcium, 9.7 mg., and serum phosphorus, 2.8 mg., per 100 cc. The carbon-dioxide-combining power was 45.9 vol. %. Alkaline phosphatase was 5.8 units. Total protein measured 5.9 gm. per 100 cc., with 3.5 gm. of albumin and 2.4 gm. of globulin. The sedimentation rate was 22.5 mm. per hour. The reaction to the Sulkowitch test on the urine was negative. Blood creatinine was 1.1 mg. and urinary creatine 90 mg. per 24 hours. Phenolsulfonphthalein excretion was 72%. The basal metabolic rate was —5%. The blood test for syphilis gave a

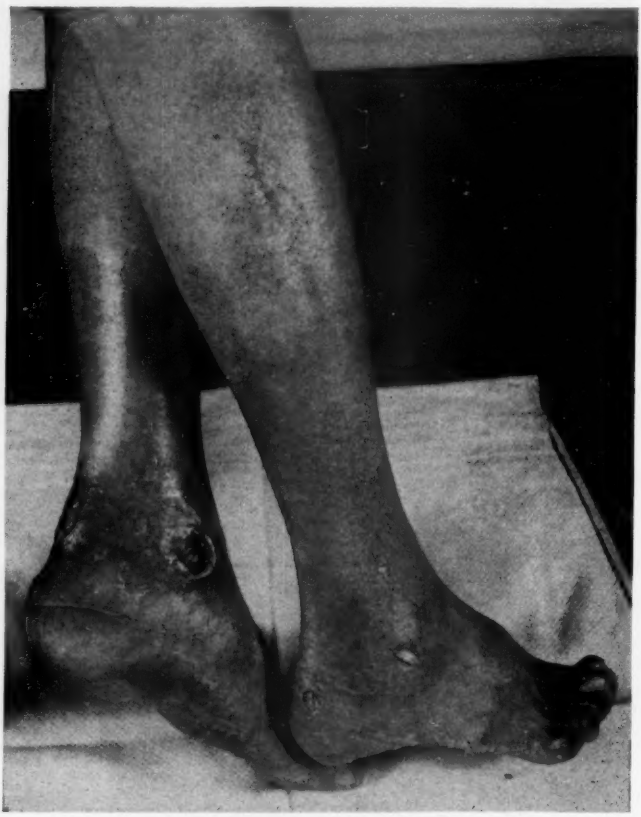

Fig. 3 (Case 1).—Lateral view of lower extremities. Ulcer over left medial malleolus can be seen, and border of the ulcer over left Achilles tendon is also perceptible. Hyperkeratotic lesion over right external malleolus and right heel can also be seen.

negative reaction. Examination of the stool revealed nothing unusual. A dextrose-tolerance test done on Oct. 1, 1951, showed the following blood sugar values: The level on fasting was 87 mg.; at one hour, 98 mg.; at two hours, 133 mg.; at three hours, 63 mg., and at four hours, 106 mg., per 100 cc. Fluoroscopy of the chest showed nothing abnormal. Roentgenographic studies revealed calcification in the right triceps tendon at its attachment to the olecranon process and in the ligaments of both sides of the knee and ankle joints. There was generalized osteoporosis of minimal degree. No evidence of calcification was present in the aorta. Lateral views of the skull showed a minimal degree of hyperostosis frontalis.

A specimen of skin from the scleroderma-like area showed the following changes: There were hyperkeratosis, acanthosis and blunting of the rete pegs and papillary bodies, decrease in the over-all thickness of the dermis, absence of hair follicles and sebaceous glands, compression of sweat glands, thickening and disorganization of the collagen bundles in a manner quite different from that seen in scleroderma, and a perivascular infiltrate in the upper dermis which consisted of plasma cells, lymphocytes, and a few reticuloendothelial cells.

CASE 2.—Mrs. K. E. was a 42-year-old white housewife. At the age of 27 she first noticed scleroderma-like changes and recurrent ulcers on her lower legs. During her thirties bilateral

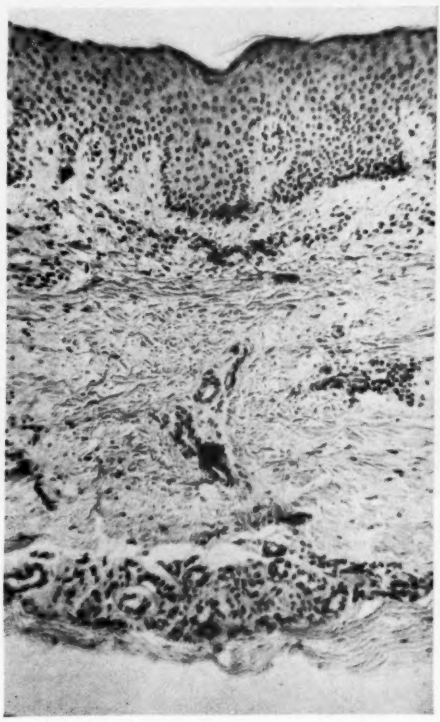

Fig. 4 (Case 1).—Low-power photomicrograph of specimen of skin removed from right leg, illustrating important microscopic features in hidebound skin of Werner's syndrome (Thannhauser [1a]; Block and Stauffer [5]; Oppenheimer, B. S., and Kugel, V. H.: Tr. A. Am. Physicians **49**:358-370 [May] 1934). Dermis is normal or slightly decreased in over-all thickness. Collagen bundles are swollen, somewhat disorderly in arrangement, and reduced in number, but there are no obliterative vascular changes. In scleroderma, with which cutaneous alterations of Werner's syndrome are confused most frequently on both clinical and microscopic grounds, dermis is increased in thickness; collagen bundles are hypertrophic, sclerotic, and densely packed, and there are notable obliterative changes in dermal vessels. Alterations in epidermis are inconstant in both Werner's syndrome and scleroderma, and diminution or absence of skin appendages is common to both.

cataracts developed, and iridectomy was carried out. Lumbar sympathectomy was performed elsewhere when the patient was 41 years of age on the assumption that she had true scleroderma of the lower extremities. No apparent benefit was derived from this procedure.

The patient's past history was not remarkable otherwise. She had a son aged 18 and a daughter aged 23, both living and well. The daughter was married and had two apparently healthy children.

Fig. 5 (Case 1).—Roentgenogram of left foot and ankle, showing calcium deposition in vicinity of calcaneus and external malleolus.

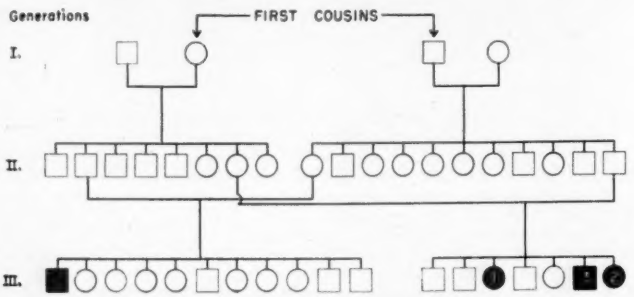

Fig. 6.—Pedigree of family described. Black numbered circles and squares indicate known persons with Werner's syndrome. Black square without a number indicates cousin who reputedly has clinical signs which suggest diagnosis of Werner's syndrome.

The diagnosis of Werner's syndrome was made in 1951, when the patient was 42 years of age. Physical examination at that time showed the following significant findings: The patient was of short stature and had a thickset trunk. The extremities were slender, and the entire skin

was dry. The skin of the ankles and feet was hidebound, and the changes resembled those of scleroderma. There were deep ulcers over the malleoli of both ankles, and movement of the feet was restricted by the hidebound skin. Both eyes showed evidence of previous iridectomy. All laboratory examinations gave normal results.

CASE 3.—E. R., an unemployed white married man aged 45, was apparently well until the age of 34. At that time bilateral cataracts developed. Shortly thereafter his scalp hair became gray, and sclerodermatous changes appeared in the skin of the feet and ankles. Painful calluses and disabling ulcers developed on the feet.

The diagnosis of Werner's syndrome was made at another hospital in 1951, when the patient was 45 years of age. Physical examination at that time showed the following significant findings: The entire integument was dry, atrophic, and wrinkled, and the skin of the hands, feet, and ankles resembled that seen in scleroderma. Ulcers were present over the malleoli of both ankles, and both eyes showed evidence of previous iridectomy. The scalp, beard, and axillary hair was sparse and gray, and the voice was high-pitched and whispering.

Laboratory examinations gave normal results.

In addition to these three patients, a double cousin reputedly has cataracts and leg ulcers (Fig. 6). No further information is available on this patient.

COMMENT

These three patients demonstrate the important clinical features of Werner's syndrome. All were looked upon as having scleroderma until the hereditary features, cataracts, bodily habitus, and features of early senility were comprehended as a group. The appearance of the syndrome in siblings with consanguineous history is well illustrated by the three cases.[7]

SUMMARY

A brief description of Werner's syndrome is presented, and three case abstracts which illustrate significant features of this syndrome are cited.

7. Thannhauser.[1a] Oppenheimer and Kugel.[1b] Carleton.[4]

ACUTE STAPHYLOCOCCIC LUNG ABSCESS CURED WITH AID OF BACITRACIN

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THIS case is presented as the first in which recovery from acute staphylococcic lung abscess may be attributed to bacitracin. While the majority of acute non-putrid lung abscesses respond well to antibiotics, the occasion may arise in which the invading organism is resistant to the common antibiotics and the infection fails to come under control.

There are reports that 59% of the strains of Staphylococcus isolated are now penicillin-resistant.[1]

REPORT OF CASE

A 62-year-old white man was admitted to the Prospect Heights Hospital on Aug. 6, 1951, with a 41-hour history of severe pain in the epigastrium and right upper abdominal quadrant of sudden onset, accompanied with nausea and vomiting.

Previous history included an acute cowper's gland abscess in July, 1951, which was successfully treated by surgery and antibiotics. The patient had been a chronic alcoholic for the past nine years, consuming daily 1 pt. to 1 qt. (500 to 1,000 cc.) of whiskey. His diet was unsatisfactory.

Physical examination on admission revealed an elderly man, acutely ill, restless, moaning with pain, and grunting with respiration. The skin was pale and dry and had a slight icteric tinge. The temperature was 101.6 F. The heart rate was 120, and the respirations were 30 per minute. The pupils, moderately contracted, were regular and equal and reacted to light and in accommodation. The sclerae were congested, watery, and slightly icteric. The mouth contained many carious teeth. Ears, nose, and throat were normal. The tongue was dry and red and covered with a brownish coat. The neck was supple. The trachea was in the midline, and no cervical nodes were palpable. The chest was symmetrical, and the respiratory movements, although shallow and jerky, were equal bilaterally. The lungs were clear to percussion and auscultation. The heart was slightly enlarged, and there were no murmurs. Heart sounds were of good quality. The blood pressure was 110 systolic and 70 diastolic. The abdomen was rigid above the level of the umbilicus. There were marked muscle rigidity and tenderness on palpation in the epigastrium and exquisite tenderness and rebound tenderness below the lower right costal border and upper part of the right rectus abdominis. No masses were felt. There was no evidence of fluid. The extremities were normal.

Laboratory studies on admission revealed a hemoglobin concentration of 78%; there were 3,530,000 red blood cells and 15,450 white blood cells with 87% polymorphonuclear leucocytes and 13% lymphocytes. The urine was dark amber and contained bile; otherwise it was normal.

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The differential diagnoses included acute cholecystitis, perforated peptic ulcer, and acute pancreatitis. It was felt that a laparotomy was indicated, and this was performed by Dr. Louis Steinger. An enlarged edematous pancreas and hydrops of the gall bladder were noted on operation. A cholecystostomy was performed and the abdomen was drained. Supportive measures, including fluids given parenterally, antibiotics, and intestinal decompression, were instituted.

On Aug. 7, the first postoperative day, the respirations became increasingly labored; the patient coughed occasionally and brought up some frothy, colorless sputum. Examination of the chest revealed dulness at both bases, more marked on the left, with diminished breath sounds and fine, moist rales. The temperature rose to 101 F.; the pulse rate was 100 and the respiration rate, 40 per minute. The patient was placed in an oxygen tent. He received fluids parenterally,

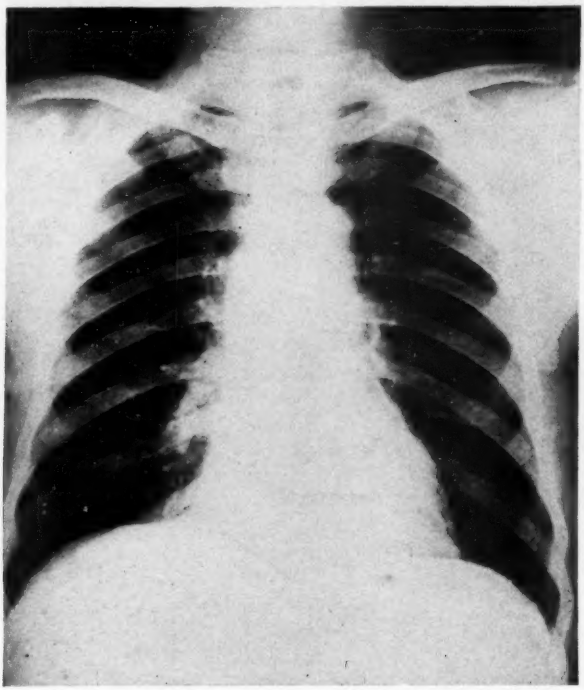

Fig. 1.—Roentgenogram taken June 28, 1951, five and one-half weeks prior to present illness. Normal lung fields. Slight left ventricular cardiac enlargement; elongation of the aorta.

vitamins, 50,000 units of aqueous penicillin every three hours, 300,000 units of procaine penicillin in oil every 12 hours, and 0.5 gm. of dihydrostreptomycin every 12 hours. All the antibiotics were administered intramuscularly. A transfusion of 500 cc. of citrated whole blood was also given.

A blood culture taken on Aug. 8, the following day, was negative for pathogens.

On the fourth postoperative day, the patient became more dyspneic, orthopneic, and cyanotic. The heart rate was 170 and totally irregular. An electrocardiogram confirmed the impression of auricular fibrillation. Quinidine sulfate was given at the rate of 6 grains (0.39 gm.) every two hours in order to restore a normal sinus rhythm. After taking 12 grains (0.78 gm.), the patient had nausea, vomiting, and severe diarrhea. The administration of quinidine sulfate was

stopped. He was quickly digitalized; the heart rate slowed, and the cardiac status improved. The heart spontaneously returned to a normal sinus rhythm eight days later.

The patient continued to cough, brought up a white mucoid sputum, and continued to run an elevated temperature (100 to 103 F.). On the 11th day postoperatively, a roentgenogram of the chest revealed a bilateral pneumonic process with an infiltration in the base of the right upper lobe and a large consolidated area in the lower one-third of the left lung. The antibiotic therapy was supplemented with chloramphenicol 500 mg. every six hours.

On the 14th hospital day, the abdominal wound broke down, with evisceration. This was repaired immediately with the patient under anesthesia induced with cyclopropane-oxygen-nitrous

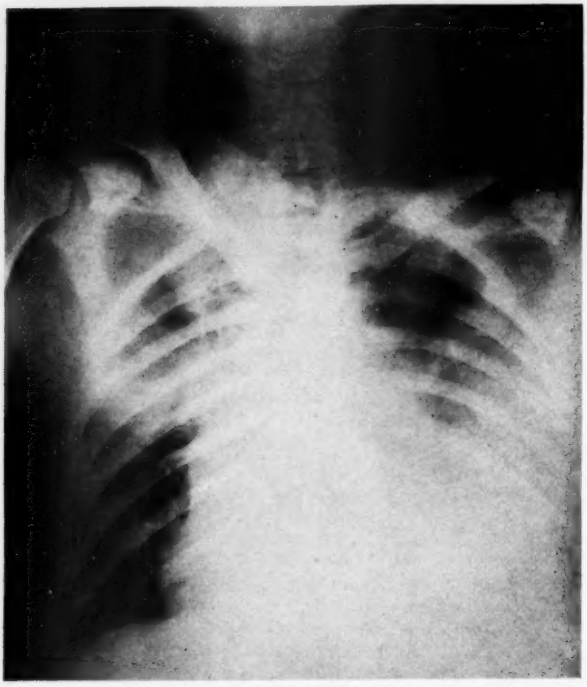

Fig. 2.—Roentgenogram made at patient's bedside on Aug. 17, 1951. Moderate-sized patch of infiltration present in base of right upper lobe. Large patch of consolidation in the left lower lobe. No gross amount of fluid demonstrated. Impression: Bilateral pneumonia, probable atelectasis.

oxide. After the operation the temperature fluctuated between 101 and 103 F. He was toxic and became disoriented. The confused state lasted for several days.

A second blood culture taken on Aug. 21 was reported as showing no pathogens.

On Aug. 22, after using streptomycin for 16 days, the patient complained of tinnitus, nausea, and faintness; therefore, this medication was discontinued. Chloramphenicol therapy was also discontinued, and terramycin administration was started at a dosage of 500 mg. every six hours.

On Aug. 24, the 18th hospital day, the cough became more frequent, and the patient began to expectorate thick, yellowish-gray, odorless, purulent sputum. Physical examination of the chest at this time revealed moist rales in the right subclavicular area with slight diminution in vocal resonance. The left base was dull to percussion. Breath sounds were distant, and there were

medium moist rales in the same area. A roentgenogram of the chest taken on this date at the bedside showed some clearing of the infiltration in the right upper lobe but little change in the base of the left lung.

During the days that followed the patient became more toxic, complained of complete exhaustion, and lost all desire for food. He would raise copious amounts of creamy, purulent sputum while lying on the right side.

On Aug. 28, direct smear of the sputum showed disintegrated polymorphonuclear leucocytes, while staphylococci were numerous. Sputum culture showed hemolytic Staphylococcus albus.

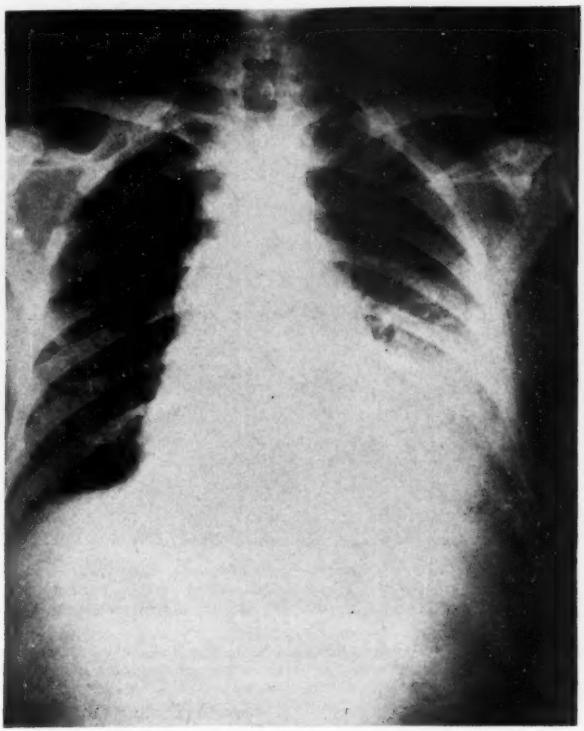

Fig. 3.—Complete resolution of the right-sided infiltration in roentgenogram taken Sept. 6, 1951. Partial resolution of the left lower lobar consolidation. Suggestive cavitation at the base lateral to the cardiac shadow. No pleural fluid. Impression: Probable pulmonary abscess.

Frequent sputum examinations failed to reveal any acid-fast bacilli. A blood count on Aug. 29 showed 3,750,000 red blood cells, 75% hemoglobin, and 28,700 white blood cells, with 72% polymorphonuclear leucocytes, 26% lymphocytes, and 2% monocytes. On Aug. 31 a transfusion of 500 cc. of citrated whole blood was given. A roentgenogram of the chest on this date revealed a clear right lung and a persistence of the infiltration in the left lower lobe. The dosage of aqueous penicillin was increased to 100,000 units every 3 hours and that of procaine penicillin in oil to 600,000 units every 12 hours. Aerosol penicillin, 50,000 units in 1 cc. of isotonic sodium chloride solution was administered three times daily. Dihydrostreptomycin therapy was started again in doses of 0.5 gm. every eight hours. Fluids were forced. Postural drainage was applied intermittently. During the following week, the condition of the patient deteriorated progressively.

He remained toxic and lethargic, took very little food, and became more emaciated. On Sept. 2 the patient was given another transfusion of 500 cc. of citrated whole blood. The physical signs in the chest remained the same. On Sept. 4 the dosage of aqueous penicillin was increased to 500,000 units every three hours. On Sept. 6, one month from the day of admission, a roentgenogram of the chest showed pleural thickening over the left lower lobe and several faintly outlined areas of decreased density which were probably due to cavitation.

On Sept. 7 another pure culture of hemolytic Staph. albus was obtained from the sputum and was tested for sensitivity against the antibiotics. Sensitivity discs with three concentrations of each of the antibiotics were used. The organism was found sensitive to the bacitracin disc of 20 units and to the aureomycin disc of 60 γ. Complete lack of sensitivity was found with penicillin,

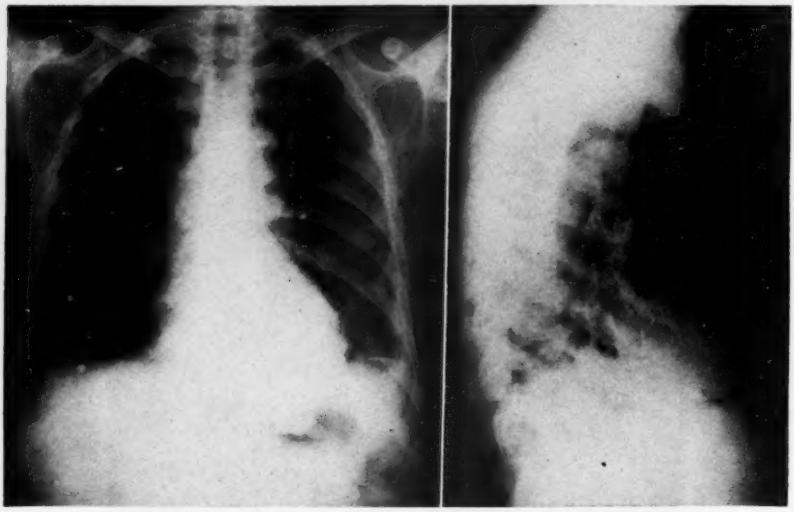

Fig. 4.—Posteroanterior and left lateral roentgenograms made Sept. 18, 1951. Further resolution of the left lower infiltration. Several thin-walled cavities present throughout lower lobe. Minimal pleurisy at left base. Impression: Pulmonary abscess, markedly improved.

dihydrostreptomycin, terramycin, and chloramphenicol. The doses of antibiotic used in testing sensitivity were as follows:

Bacitracin, 2, 10, 20 units	Dihydrostreptomycin, 0.5, 1.0, 10 γ
Aureomycin, 10, 30, 60 γ	Terramycin, 10, 30, 60 γ
Penicillin, 0.5, 1.0, 10 units	Chloramphenicol, 10, 30, 60 γ

On Sept. 9 administration of the previously used antibiotics was discontinued. Aureomycin was given in doses of 500 mg. every six hours. On Sept. 11 sulfadiazine was given in an initial dose of 3 gm., followed by 1 gm. every four hours. In the next few days the patient continued to grow worse. The temperature fluctuated between 99 and 101 F. The cough and expectoration persisted. The physical signs in the chest remained unchanged.

On Sept. 14, five weeks after the onset of the pulmonary complication, roentgenograms of the chest showed evidence of some infiltration, with several thin-walled cavities present throughout the left lower lobe. On this date the intramuscular administration of bacitracin was started. Treatment with aureomycin and sulfadiazine was discontinued. Bacitracin was given in dosage of 10,000 units every four hours for the next seven days. In 48 hours the temperature subsided to 99 F. The patient said he felt better and had lost his feeling of exhaustion; the appetite returned, and he also took intercibal feedings. The cough and expectoration began to diminish, and one week

after the start of bacitracin therapy they had completely disappeared. Two days after the start of the bacitracin treatment chest findings began to show improvement. The dulness in the left base diminished, and breath sounds became more audible. A roentgenogram of the chest on Sept. 18, one week after the start of treatment with bacitracin, disclosed some pleural thickening at the left base. The infiltration in the left lower lobe showed marked resolution.

While the patient was receiving bacitracin therapy, daily urines were examined. On Sept. 17, after three days of intramuscular administration of bacitracin, the urine, which had always been normal, had a specific gravity of 1.011, contained many red blood cells, and showed a 2 + reaction for albumin. After one week of bacitracin therapy, on Sept. 21, the additional finding of a trace of sugar in the urine was reported, and the dosage was reduced to 10,000 units every eight hours and was maintained at this level for the next 14 days. The patient received a total of 830,000 units. During this period, the urines contained traces of albumin and occasional traces of sugar. Polyuria was noted. A Mosenthal test was done on three occasions, the first on Oct. 3, while the patient was receiving bacitracin, the second on Oct. 9, and the third on Oct. 26, the last two

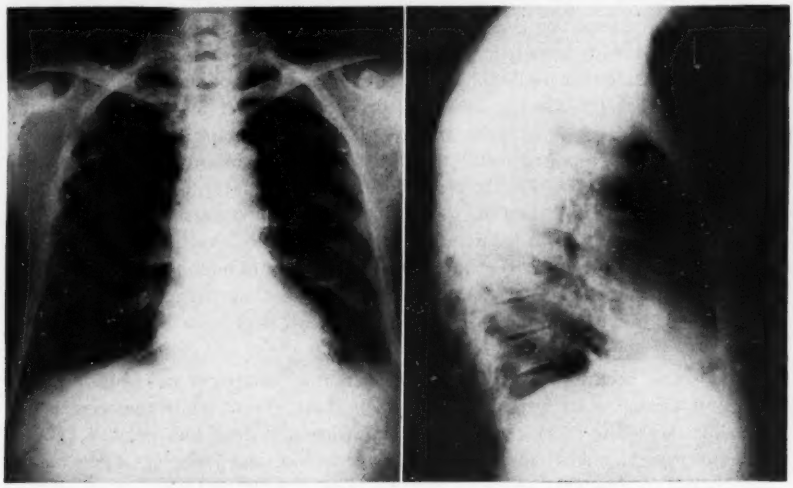

Fig. 5.—Posteroanterior and left lateral roentgenogram made Oct. 5, 1951. Complete resolution of the inflammatory process at the left base. Residual fibrotic or atelectatic lobules in the left lower lobe. Pulmonary cavities not visible. Still some pleural thickening at the left base. No pleural fluid. Conclusion: Resolved pulmonary abscess; minimal pulmonary fibrosis in left lower field; fibrous pleurisy in left field.

being done 5 and 22 days, respectively, after bacitracin treatment had been discontinued. The first test showed a maximum concentration of 1.014, a minimum concentration of 1.003, and nocturnal polyuria (1,735 cc. from 8 p.m. to 8 a.m.). The second test showed a maximum concentration of 1.021, a minimum concentration of 1.003, and a nocturnal polyuria (1,730 cc.). The third test showed a maximum concentration of 1.025, a minimum concentration of 1.015, and a nocturnal urinary volume of 510 cc. The last urine collected gave negative reactions for albumin and sugar. The microscopic examination showed nothing abnormal. Urine specimens that reduced Benedict's reagent failed to ferment yeast.

On Sept. 26, while the patient was receiving bacitracin, a sulfobromophthalein (bromsulphalein®) sodium liver function test was done to determine the possibility of liver damage. Fifteen per cent of the dye was retained five minutes after injection, and none was retained after 30 minutes.

Repeated examinations showed normal values for blood sugar and urea nitrogen.

The patient continued to recover. His gain in weight and strength was rapid. Twenty-two days after starting bacitracin therapy, on Oct. 5, his chest was clear to percussion and auscultation. A roentgenogram of the chest on this date showed some pulmonary fibrosis in the left base.

On Oct. 13, the 69th hospital day, the patient was discharged as cured.

COMMENT

The diagnosis of staphylococcic lung abscess may be difficult to make. In this patient postoperative atelectasis developed in the right upper and left lower lobes. The following factors favored this diagnosis: (*a*) major surgical procedure in the upper abdomen with its subsequent diminished depth of respiration; (*b*) the onset of pulmonary complication 24 hours postoperatively; (*c*) the expectoration of frothy, colorless, and odorless sputum, later becoming thick and mucoid (until the development of the secondary infection).

The atelectasis in the right upper lobe showed improvement in two and a half weeks and was completely cleared in three weeks. The atelectatic left lower lobe became infected with hemolytic Staph. albus and went on to abscess formation. One must conclude that the Staphylococcus was the offending organism in the lung abscess, and that the abscess subsided through the effect of bacitracin for the following reasons: (*a*) the pure culture of hemolytic Staph. albus obtained by sputum culture on repeated tests; (*b*) the response of the organism to the antibiotics in vitro as in vivo; (*c*) the persistence of toxemia, fever, cough, and purulent expectoration and the constant physical findings in the chest over a period of several weeks, unchanged by the administration of various antibiotics in large doses, and followed by dramatic improvement in 48 hours on intramuscular treatment with bacitracin (it has been shown that bacitracin injected intravenously into rabbits appears in high concentration in the lungs, one, two, and three hours after injection [2]).

There have been reports of nephrotoxic action by bacitracin and of its reducing action on urine.[3] Our patient showed both these effects while receiving larger doses (10,000 units every four hours), but when the dose was reduced (10,000 units every eight hours) the albuminuria, hematuria, and reducing action on the urine began to diminish. Kidney function tests showed the presence of nephrotoxicity, which completely disappeared three weeks after discontinuing the use of bacitracin. It is believed that the manifestations of the nephrotoxic action of the

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bacitracin are evidences of a depression of tubular function and possibly glomerular function.[4] The nature of the reducing substance has not been established, although it has been determined that it is neither a sugar nor bacitracin itself.[5]

It is important that bacitracin be considered in therapy of those infections that are resistant to the other antibiotics. In serious infections, in cases in which the organism is available in pure culture, one should test for sensitivity to the various antibiotics. This will save valuable time and will reduce both morbidity and mortality. In the absence of any previous renal damage in the patient, the nephrotoxic action of bacitracin is not a contraindication to its use.

SUMMARY

This is a report on the first case of acute staphylococcic lung abscess cured by intramuscular administration of bacitracin. Bacitracin was found to be effective after large doses of penicillin, terramycin, chloramphenicol, dihydrostreptomycin, aureomycin, and sulfadiazine had failed to halt the infection. The txoic effects of bacitracin are briefly discussed.

Prospect Heights Hospital.

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ESCHERICHIA COLI ENDOCARDITIS

Report of a Case Presenting a Difficult Problem in Chemotherapy

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ST. LOUIS

WELL-AUTHENTICATED instances of endocarditis due to Escherichia coli are uncommon, only 14 such cases having been reported.[1] All these cases have met the logical criteria suggested by Harries and Burtenshaw [1e] and by Hoffman and associates,[1i] namely: (1) positive blood cultures obtained during the life of a patient with a compatible clinical picture and (2) demonstration of the organism in the cardiac valves at necropsy.

Two additional patients with this condition have been reported on, both of whom recovered after streptomycin therapy.[2] For these patients the diagnosis was made on the basis of clinical evidence plus positive blood cultures. Recoveries following other types of antibiotic therapy have not been recorded. It seems reasonable that, with newer antibiotic agents, more successful results will be reported in the future. In these circumstances, cases satisfying the first criterion would have to be accepted as proved. Microscopic examination of the heart valves in successfully treated patients might be expected to show healing or healed vegetations containing no bacteria.

The case reported here is presented as one of Esch. coli endocarditis in which both the heart valve and the blood stream were sterilized during the life of the patient, death being due to intercurrent hepatic insufficiency.

From the Departments of Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital.

Dr. Ross is Assistant in Clinical Medicine; Dr. Wheeler is Resident in Pathology, and Dr. Hagemann is Assistant Professor of Clinical Medicine.

1. (*a*) Crawford, A. M., and Cruickshank, R.: A Case of Infective Endocarditis Due to Bacillus Coli, Glasgow M. J. **122**:21-24 (July) 1934. (*b*) Dickar, L.: Acute Bacterial Endocarditis Due to Bacterium Acidilactici, Arch. Int. Med. **49**:788-798 (May) 1932. (*c*) Duhig, J. V.: Septicemia and Acute Infective Endocarditis Due to Bacterium Coli, M. J. Australia **1**:435-437 (April 8) 1933. (*d*) Fletcher, D. E.: Bacillus Coli Endocarditis: Review of the Literature with Report of a Case, Am. Heart J. **34**:743-750 (Nov.) 1947. (*e*) Harries, G. E., and Burtenshaw, J. M. L.: Acute Infective Endocarditis Due to Bacterium Coli, Lancet **2**:803-804 (Oct. 2) 1937. (*f*) Horder, T. J.: Infective Endocarditis, with an Analysis of 150 Cases and with Special Reference to the Chronic Form of the Disease, Quart. J. Med. **2**:289-324 (April) 1909. (*g*) Phipps, C.: Acute Bacterial Endocarditis, New England J. Med. **207**:768-770 (Nov. 3) 1932. (*h*) Smith, A. G.: Endocarditis Due to Escherichia Coli, ibid. **243**:129-131 (July 27) 1950. (*i*) Hoffman, M. S.; Wellman, W. E., and Sayre, G. P.: Escherichia Coli Endocarditis: Report of a Case, Proc. Staff Meet., Mayo Clin. **26**:1-8 (Jan. 3) 1951.

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CLINICAL HISTORY

P. P. (193378), a 72-year-old white woman, entered Barnes Hospital on Jan. 27, 1951, and died March 23, 1951.

History.—The patient recalled no serious illness and seemed in good health all her life. At the age of 55 she was told by her physician that she had a heart murmur. Subsequently, signs of mitral stenosis were noted, and she received digitalis because of dyspnea and slight ankle edema. Three days prior to her admission, the patient rather suddenly displayed shaking chills, fever, marked dyspnea, and a nonproductive cough. These symptoms persisted until the time of her admission.

Results of Physical Examination.—The temperature was 104.5 F. (40.3 C.); the pulse rate was 112; the respiratory rate was 20 per minute, and blood pressure was 100/72. The patient appeared acutely ill. Respirations were rapid, but there was no cyanosis. Bronchovesicular breath sounds were heard over the left lung base, along with moist inspiratory rales. The

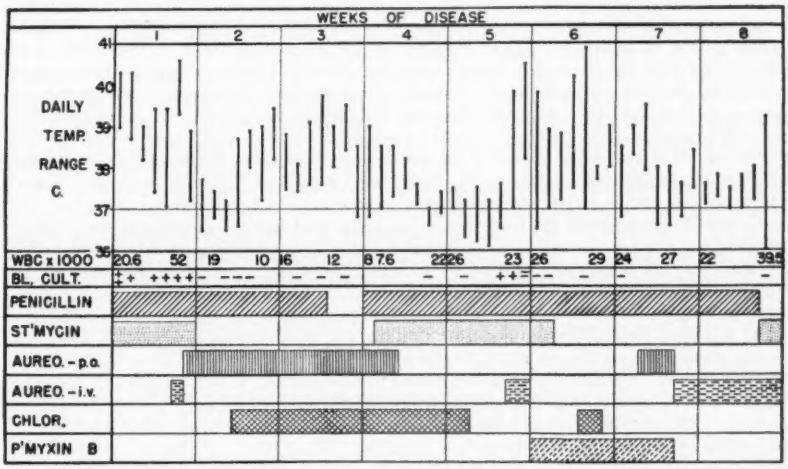

Fig. 1.—Course of disease. Antibiotic therapy is charted qualitatively. *Chlor.* means chloramphenicol.

heart borders could not be outlined; the cardiac rhythm was regular, and no murmurs were heard. No abdominal masses or organs were palpable. There was a slight amount of pitting edema of the ankles.

Laboratory Data.—Studies of blood revealed a red blood cell count of 4,980,000, a hemoglobin concentration of 15.3 gm. per 100 cc., and a white blood cell count of 20,600. The differential count showed 2% juvenile forms, 11% stab forms, 76% segmented forms, 9% lymphocytes, and 2% monocytes. Urinalysis disclosed no abnormality except for a 4+ reaction for albumin and 15 to 20 white blood cells per high-power field. A guaiac test on a stool specimen gave a negative reaction. The Kahn reaction was negative. Nonprotein nitrogen was 61 mg. per 100 cc. Sputum contained Type III Pneumococcus on direct typing with antiserum, but the culture was overgrown with coliform organisms. A chest roentgenogram revealed cardiac enlargement, left auricular prominence, pulmonary congestion, and blunting of the left costophrenic angle. The electrocardiogram showed a P-R interval of 0.24 second, sinus mechanism, low T waves in Lead I and Lead AVF, and an inverted T wave in Lead II.

Hospital Course (Fig. 1).—Intramuscular administration of penicillin, 200,000 units every three hours, and of streptomycin, 0.5 gm. every six hours, was started immediately. Oxygen therapy was instituted, and digitalis treatment was continued. On the second hospital day, a direct smear of the broth from an admission blood culture revealed Gram-positive diplococci

which were not typed. The patient's temperature gradually declined to 100.4 F. (38 C.) in the first three days and the blood pressure averaged 80/60. The signs in the left chest remained unchanged, and methamphetamine (desoxyephedrine) hydrochloride was used, as necessary, to maintain blood pressure. After the fourth hospital day, the temperature showed daily elevation to 102.2 to 104 F. (39 to 40 C.). This septic fever continued for the remainder of the first week. The patient exhibited an acute psychosis, and the leucocyte count rose to 52,000. The cerebrospinal fluid was entirely normal. On the fourth hospital day, two admission blood cultures were reported positive for Esch. coli, the Pneumococcus apparently having been overgrown. Sensitivity studies on this organism indicated that growth was inhibited by the following antibiotic concentrations:

Aureomycin	0.0005
Chloramphenicol	0.005
Terramycin	0.03
Streptomycin	0.03

Intravenous aureomycin therapy was begun in a dose of 500 mg. every six hours. Within 24 hours, there was a striking clinical improvement, and the temperature fell to 99 F. (37.2 C.). For the first time since admission, apical systolic and diastolic murmurs characteristic of mitral stenosis and insufficiency were heard. Streptomycin therapy was discontinued, and aureomycin in an oral dose of 3 gm. a day was substituted for parenteral therapy. The use of penicillin was continued.

During the second week, the white blood cell count declined to 10,000, and the pulse rate fell to 80 per minute. Blood cultures, which had been positive for Esch. coli on seven occasions during her first six hospital days, became sterile coincident with clinical improvement.

On the 11th hospital day, the temperature rose again. Because of severe nausea and vomiting (thought to be due to aureomycin), oral administration of chloramphenicol (chloromycetin®), 750 mg. every six hours, was started. At this time one splinter hemorrhage was noted on the left forefinger. In addition, a very rough systolic murmur, which had not been heard previously, was audible in the fourth interspace to the left of the sternum. A gallop rhythm developed. Blood and urine cultures remained sterile. Candida was cultured from the sputum. The chest roentgenogram was unchanged, and fluid aspirated from the left side of the chest was sterile on culture. The third week was characterized by irregular swinging fever. During this week the patient received 800,000 units of penicillin, 3 gm. of chloramphenicol, and 2 gm. of aureomycin each day. Blood cultures remained sterile. Despite elevation in temperature to 102.2 F. (39 C.), the patient felt improved in that she ate well, appeared stronger, and was rational. The leucocyte count remained at about 12,000 to 16,000. Penicillin therapy was discontinued.

During the fourth hospital week, the temperature elevations continued for the first three days, but then the fever gradually subsided after penicillin and streptomycin therapy was reinstituted. Other than the presence of a few rales at the left lung base, the persistence of the apical systolic and diastolic murmurs, and the systolic murmur in the fourth interspace adjacent to the sternum, no significant physical signs were noted. Blood cultures remained sterile. Aureomycin administration was discontinued because of vomiting. The patient appeared worse, although the temperature remained normal and the leucocyte count fell to 7,300. Feeding became a severe problem. A plastic feeding tube was inserted on several occasions, but the patient resisted actively, and parenteral alimentation was used.

At the end of the fifth week, the temperature rose to 102.2 F. (39 C.) without obvious cause. The patient became lethargic and irrational. Blood cultures showed coliform organisms to be present again. No organisms were demonstrated on repeated urine or sputum cultures, and only a rare red blood cell was seen in the urinary sediment. Sensitivity tests done on the Esch. coli from the blood revealed that growth was inhibited by the following antibiotic concentrations:

	Mg./Cc.
Aureomycin	0.002
Chloramphenicol	0.004
Terramycin	0.001
Streptomycin	>0.05
Sulfadiazine	>1
Polymyxin B	<0.0005

With the return of the bacteremia, the white blood cell count rose to 22,000. The patient was again given aureomycin intravenously, 500 mg. every six hours, in addition to penicillin and streptomycin. With the continued fever, the intravenous medication precipitated attacks of acute pulmonary edema. For this reason, and because of the lack of clinical response, aureomycin therapy was discontinued, and intramuscular administration of polymyxin B, 40 mg. every six hours, was begun. This drug also had little effect on the fever, and the patient continued to have repeated attacks of pulmonary edema. Hydration was maintained with subcutaneous administration of fluids, although provision of an adequate caloric intake was impossible. The temperature rose to 105.4 F. (40.8 C.); the patient became lethargic, incontinent, and irrational. By the end of the week, it was apparent that the systolic murmur in the fourth left interspace was being transmitted from the mitral area. A small hemorrhage was noted in the right conjunctiva, but no other embolic signs were noted, and the spleen could not be felt.

In the seventh week, use of polymyxin was discontinued and intravenous administration of aureomycin (0.5 gm. every six hours) was reinstituted through an indwelling polyethylene catheter. Considerable numbers of red and white blood cells and a reaction for albumin were noted in the urine. The temperature fell below 100.4 (38 C.), and blood cultures remained sterile. Three days before the patient's death, a thrombophlebitis developed at the site of the indwelling venous catheter. Progressive jaundice was noted. There was tenderness in the right upper quadrant of the abdomen, but the liver was not palpable. An open roentgenogram of the abdomen was unrevealing. Liver-function tests showed 6.08 mg. of sodium bilirubinate and 2.36 mg. of bilirubinglobin per 100 cc. Cephalin flocculation was 3+; thymol turbidity, 0.8 unit, and alkaline phosphatase, 3 Bodansky units.

Severe muscle pain and tenderness developed. The white blood cell count rose to 40,000. The patient went into peripheral vascular collapse, which failed to respond to numerous pressor agents, and she died quietly on the 56th hospital day.

Gross Autopsy Observations.—An autopsy was performed two hours after death. The body was that of a deeply jaundiced white woman, 72 years of age, measuring 176.5 cm. in length and weighing 63 kg.

The peritoneal and pleural cavities were moist, but contained no measurable amount of fluid. The pericardial cavity contained 35 cc. of icteric fluid.

Heart and Lung: The heart was moderately enlarged and weighed 400 gm. (maximum normal weight, 295 gm.). The tricuspid valve and the endocardium of the left atrium were thickened. The mitral valve was represented by a thick, nonpliable, circular membrane with a central orifice, the buttonhole valve of advanced mitral stenosis. On the atrial surface of the posterior portion of the mitral membrane, there was a broad, flat, mottled, brown, friable thrombus measuring 23 by 15 by 4 mm. The thrombus had extended to involve the chordae tendineae and the ventricular surface of the mitral membrane. Slight fibrous adhesions were between the cusps of the aortic valve. There was a moderate sclerosis of the coronary arteries. The lungs weighed 610 gm. Slight bronchiectasis was present in the lower lobes.

Abdominal Organs: The liver weighed 1,780 gm. The capsule was smooth, and the margins were slightly rounded. The cut surface bulged moderately and was icteric, soft, friable, and greasy. No alterations in the architectural markings were seen. The wall of the gall bladder was thickened, and the lumen contained many faceted stones. The hepatic, cystic, and common bile ducts were patent. The spleen was not remarkable. The kidneys were the seat of slight arteriolar nephrosclerosis. The renal pelves, ureters, and urinary bladder were not unusual.

Brain: The brain contained a focus of old encephalomalacia 8 mm. in diameter in the anterior portion of the right caudate nucleus.

The organs that were not mentioned were not considered to be the seat of significant disease.

Microscopic Observations.—Heart: There was no evidence of acute rheumatic fever. The myocardium contained a few small areas of focal fibrosis. Sections of the mitral valve and chordae tendineae revealed an acute and subacute endocarditis. In some areas the innermost zone of the vegetation was composed of necrotic debris immediately adjacent to the valve substance, while in other areas the inner layer consisted of young connective tissue containing numerous capillary vessels and a diffuse infiltrate of lymphocytes and polymorphonuclear leucocytes. Overlying both types of inner zones was a layer of fibrin containing a moderate number

of polymorphonuclear leucocytes and erythrocytes (Fig. 2). Multiple sections of the valve and vegetation, stained with eosin-methylene blue and Goodpasture modification of the Gram stain, failed to establish the presence of bacteria.

Lungs: Multiple sections were examined, and no evidence of pneumonia was found.

Liver: There was an advanced fatty metamorphosis involving the entire liver; however, the parenchymal cells in the periphery of some of the lobules were less involved (Fig. 3). An occasional bile thrombus was encountered within the lobes. Necrosis of parenchymal cells was not observed.

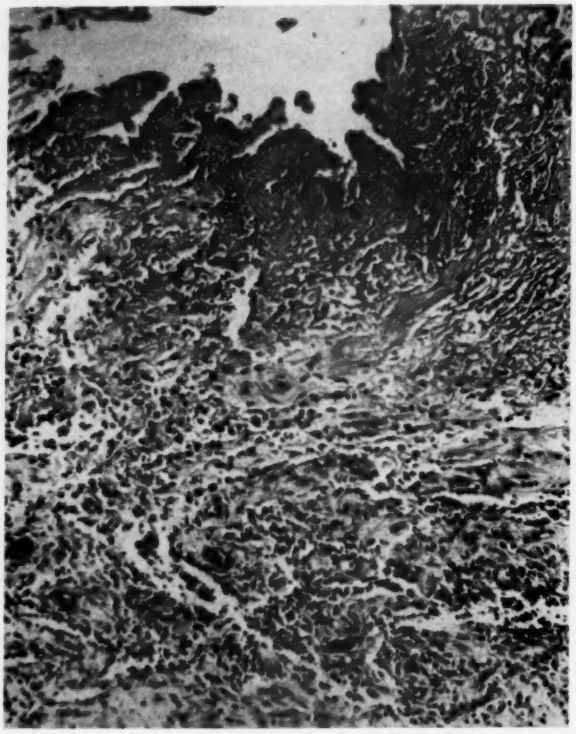

Fig. 2.—Mitral valve. There is partial organization of the thrombus. Hematoxylin and eosin stain; × 75.

Kidneys: Slight arteriolar nephrosclerosis, with complete fibrosis of scattered glomeruli, was seen. There were no lesions that could be identified as those of focal embolic glomerulonephritis. Sudanophilic vacuoles were seen in the epithelium of the proximal convoluted tubules and the loops of Henle.

There were no lesions other than that of the mitral valve that could be considered to be caused by Esch. coli.

Bacteriologic Studies.—There were no Gram-negative organisms recovered from the mitral vegetation. Micrococcus pyogenes var. albus and an unidentified Streptococcus were grown, but these were believed to be contaminants, especially since they were not demonstrable on the histologic sections.

Pathologic Diagnoses.—The pathologic diagnoses were as follows: (1) chronic endocarditis of the mitral valve, advanced with calcification and stenosis, and chronic endocarditis of the

tricuspid valve, moderate; (2) hypertrophy and dilatation of the heart; (3) acute and subacute endocarditis (history of a clinical diagnosis of bacterial endocarditis caused by Esch. coli and treatment with antibiotics; no Gram-negative bacteria demonstrable in valve by culture or microscopic examination), and (4) fatty metamorphosis of the liver, advanced, with bile stasis.

COMMENT

It seems clear on the basis of the antemortem bacteriologic data and the postmortem findings that the mitral valve of this patient was the site of Esch. coli endocarditis. The usual portals of entry for this organism are the gastrointestinal tract,

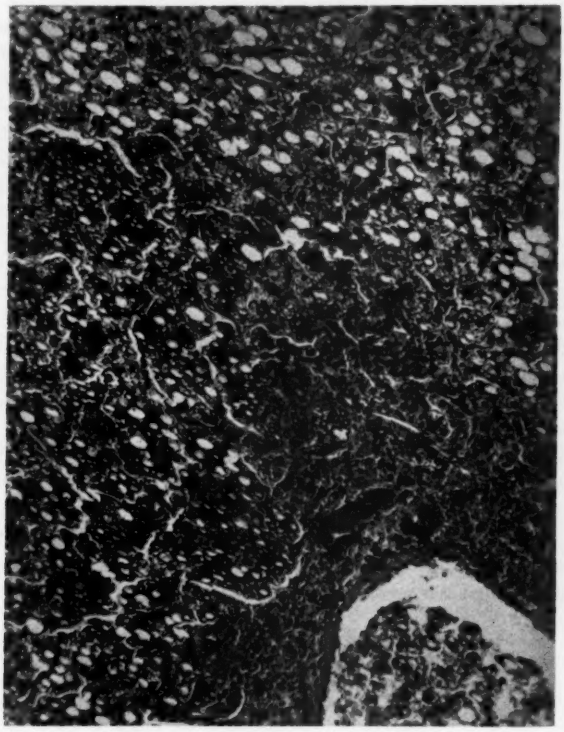

Fig. 3.—Liver, advanced fatty metamorphosis. Hematoxylin and eosin stain; × 90.

urinary tract, or the female genital organs. None of these organ systems could be indicted in this case, and a mixed pulmonary infection with Type III Pneumococcus and Esch. coli seems to have been the source of the initial bacteremia.

It is often advisable to use a combination of penicillin and streptomycin, or such agents as terramycin, chloramphenicol, or aureomycin, in the therapy of acute bacterial pneumonia in order to provide a wide range of coverage against many bacterial organisms. In spite of penicillin and streptomycin therapy in this case, bacteremia persisted, and the bacterial endocarditis developed on a previously damaged heart

valve. For this reason additional agents were employed, but the exact role of each antibiotic cannot be ascertained. Aureomycin was given intravenously on three occasions, with bacteriologic evidence of sterilization of the blood stream in two instances.

Streptomycin resistance developed during the course of therapy, at least twice as much drug being required to inhibit the growth of the infecting organism after five weeks of therapy. Although the organism was very sensitive to polymyxin B in vitro, the clinical result obtained in the use of this drug was most disappointing. The effectiveness of chloramphenicol was difficult to evaluate.

With the use of several antibiotic agents simultaneously, antibiotic synergism or antagonism is distinctly possible.[3] In one case, staphylococcal endocarditis [4] was successfully treated by a combination of agents acting synergistically. The end-result in this case might have been more successful if sensitivity tests using combinations of drugs had been carried out and the results utilized as a guide for therapy.

The difficulties involved in practical antibiotic therapy are indicated clearly in this patient. Oral therapy became impossible because of severe nausea and vomiting. Marked resistance on the part of the patient prevented use of a stomach tube, and thrombophlebitis and the threat of acute pulmonary edema seriously handicapped efforts at intravenous therapy. In spite of these handicaps, a "bacteriologic cure" was effected in this case.

Fatty metamorphosis of the liver, a lesion totally unrelated to the patient's heart disease, seemed to be the immediate cause of death. Presumably the hepatic insufficiency was the direct result of intensive aureomycin therapy. This medicament was given intravenously in a dosage of 2 gm. per day on three separate occasions, a dosage now considered excessive for this route of administration. Aureomycin, chloramphenicol, and terramycin have been reported [5] to produce fatty infiltration in the liver in experimental animals. Aureomycin and terramycin in large doses are known to cause a similar lesion clinically.[6] These reports of hepatic insufficiency resulting from intensive antibiotic therapy appeared in the literature some time after this patient was treated. Even if this information had been available at the time, intensive antibiotic therapy seemed obligatory, since the infection was poorly controlled during the first five weeks of the illness.

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3. Gunnison, J. B.; Jawetz, E., and Coleman, V. R.: The Effect of Combinations of Antibiotics on Enterococci in Vitro, J. Lab. & Clin. Med. **36**:900-911 (Dec.) 1950. Jawetz, E.; Gunnison, J. B.; Speck, R. S., and Coleman, V. R.: Studies on Antibiotic Synergism and Antagonism: The Interference of Chloramphenicol with the Action of Penicillin, A. M. A. Arch. Int. Med. **87**:349-359 (March) 1951. Gunnison, J. B.; Coleman, V. R., and Jawetz, E.: Interference of Aureomycin and Terramycin with the Action of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. **75**:549-552 (Nov.) 1950.

4. Jawetz, E.; Gunnison, J. B., and Speck, R. S.: Antibiotic Synergism and Antagonism, New England J. Med. **245**:966-969 (Dec. 20) 1951.

5. Lepper, M. H.; Zimmerman, H. Z.; Carroll, E. R., Jr.; Spies, H. W.; Wolfe, C. K., and Dowling, H. F.: Effect of Large Doses of Aureomycin, Terramycin, and Chloramphenicol on Livers of Mice and Dogs, A. M. A. Arch. Int. Med. **88**:284-295 (Sept.) 1951.

6. Lepper, M. H., and others: Effect of Large Doses of Aureomycin on Human Liver, A. M. A. Arch. Int. Med. **88**:271-283 (Sept.) 1951. Sborov, V. M., and Sutherland, D. A.: Fatty Liver Following Aureomycin and Terramycin Therapy in Chronic Hepatic Disease, Gastroenterology **18**:598-605 (Aug.) 1951.

While the outlook for patients with Esch. coli endocarditis would appear to be improving with the advent of the newer chemotherapeutic agents, other factors limiting therapy may continue to keep recovery at a relatively low rate. In the present case, the endocarditis was apparently controlled by antibiotic therapy, the patient finally dying of hepatic insufficiency.

SUMMARY

A patient is described who had Escherichia coli endocarditis superimposed on an old rheumatic valvulitis. This infection was uncontrolled during the initial weeks of intensive and combined antibiotic therapy. Terminally the patient exhibited marked hepatic insufficiency, presumably as a complication of the therapy. There was no evidence of persistent bacterial infection of the heart valve at postmortem examination. Problems arising during the course of this therapy are described.

COARCTATION OF THE AORTA

Rupture Through a "Jet Lesion" Distal to the Point of Coarctation

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THE PURPOSE of this presentation is to report a rather uncommon complication of coarctation of the aorta in a 23-year-old man. This complication consisted of the presence of a "jet lesion" in the descending aorta just distal to the point of coarctation which resulted in a localized weakening of the aortic wall with the production of a saccular aneurysm that ultimately ruptured, resulting in death. As far as we are aware, only 11 such cases have been previously reported. The presence of such a complication represents another argument for the early diagnosis of this anomaly because of the recent development of surgical measures [1] for its correction, application of which will prevent the many serious complications that this lesion entails.

In the 200 cases of coarctation of the aorta of the adult type collected by Abbott,[2] rupture of the aorta proximal to the coarctation occurred in 33 cases and distal to the coarctation in 5. Abbott suggested that the following factors are operative in producing rupture distal to the coarctation: 1. The bulbous dilatation commonly present just below the stenosis at the point of entrance through the upper aortic intercostal vessels is often thin-walled and atheromatous, as in the case reported by Leudet.[3] 2. Traction by the ligamentum arteriosum, which in coarctation is often a long, tough, fibrous cord, produces at the point of attachment a kinking and pouching that may rupture externally, as in the case of Kriegk [4] and in that of Mönckeberg.[5]

From the Division of Cardiology, Philadelphia General Hospital, and the Robinette Foundation, University of Pennsylvania.

1. Alexander, J., and Byron, F. X.: Aortectomy for Thoracic Aneurysm, J. A. M. A. **126**: 1139, 1944. Blalock, A., and Park, E. A.: Surgical Treatment of Experimental Coarctation (Atresia) of Aorta, Ann. Surg. **119**:445, 1944. Crafoord, C., and Nylin, G.: Congenital Coarctation of Aorta and Its Surgical Treatment, J. Thoracic Surg. **14**:347, 1945. Gross, R. E., and Hufnagel, C. A.: Coarctation of the Aorta: Experimental Studies Regarding Its Surgical Correction, New England J. Med. **233**:287, 1945.

2. Abbott, M. E.: Coarctation of the Aorta of the Adult Type: II. A Statistical Study and Historical Retrospect of 200 Recorded Cases, with Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of 2 Years, Am. Heart J. **3**:574, 1928.

3. Leudet, E.: Recherches anatomiques et cliniques sur le retrecissement de l'aorte au niveau du canal arteriel, Gas. méd. Paris **13**:44, 1858.

4. Kriegk, M.: Drei neue Fälle von Stenose der Aorta in der Gegend der Insertion des Ductus botalli, Vrtljschr. prakt. Heilk. Prague **137**:47, 1878; Case 2 (Barie's Observation 85).

5. Mönckeberg, J. G.: Einige Komplikationen bei angeborener Stenose des Isthmus der Aorta, Verhandl. deutsch. path. Gesellsch. **11**:267, 1908; Case 1.

In the other two cases [6] collected by Abbott, the cause of the rupture in this situation was not clear. Of this group the first case [8] probably belongs in the category of the so-called jet lesion. Moragues and associates [7] reported a case of coarctation of the aorta with rupture of the wall below the point of constriction and reviewed five additional cases from the literature [8] which were not included in Abbott's series. They came to the conclusion that "back pressure plays an important role in the mechanism of rupture of the wall below the site of coarctation," although they noted that there may be a certain weakening of the wall of the aorta in the region of the coarctation.

In a series of 104 autopsied cases of "adult-type" coarctation, Reifenstein, Levine, and Gross [9] found that the causes of death in 74% were rupture of the aorta, bacterial endocarditis or aortitis, congestive failure, or an intracranial lesion.

Rupture of Aorta Below the Point of Coarctation

Author; Date	Sex	Age, Yr.	Organ into Which Aorta Ruptured
Leudet, 1858 [8]	F	37	Left bronchus
Kriegk, 1878 [4]	M	48	Mediastinum and left pleural cavity
Mönckeberg, 1907 [8]	F	26	Left pleural cavity
Willigk, 1853 [6a]	F	36	?
Fawcett, 1905 [6b]	F	41	Pericardium, left pleural cavity, mediastinum
Goodson, 1937 [8b]	M	16	Small bronchus (left)
Bargi, L.: Clin. med. ital. **65**:152, 1934	?	?	Esophagus
Moragues, Moore, and Rossen, 1942 [7]	M	11	Esophagus
Barsantini, J. C., and Bazzano, J. J.: Arch. urug. med. **13**:448, 1938	?	?	Esophagus and left bronchus
Zaslow, J., and Krasnoff, S. O.: Am. Heart J. **26**:832, 1943	M	25	Left pleural cavity
Hecker, 1939 [8c]	M	68	Dissecting aneurysm to within 1½ in. of the bifurcation of the abdominal aorta; died of self-inflicted wounds two wk. after dissection

In this series there were 24 instances of rupture of the aorta (23%), in 19 of which the rupture occurred in the ascending aorta and in 5 in the descending aorta just distal to the coarctation. In 1948 Edwards and co-workers [10] described a localized lesion of the interior of the aorta, distal to the coarctation, which was characterized by a corrugated patch that projected above the intimal surface and microscopically

6. (*a*) Willigk, A.: Angeborene Enge des Arcus aortae, Vrtljschr. prakt. Heilk. Prague **38**:19, 1853 (Barie's Observation 39). (*b*) Fawcett, J.: Coarctation of the Aorta, Guy's Hosp. Rep. **54**:12, 1905; Case 5, p. 14.

7. Moragues, V.; Moore, L. T., and Rossen, J. A.: Coarctation of the Aorta, with Rupture of the Wall Below the Point of Constriction, Am. Heart J. **24**:828, 1942.

8. (*a*) Benkwitz, K. B., and Hunter, W. C.: Combined Infantile and Adult Coarctation of the Aorta with Coincident Occlusion of the Vena Cava Superior, Am. J. Path. **13**:289, 1937. (*b*) Goodson, W. H., Jr.: Coarctation of the Aorta: Two Unusual Cases, New England J. Med. **216**:339, 1937. (*c*) Hecker, J. T.: Coarctation of the Aorta: Report of a Case with Rupture Distal to the Constriction, J. Iowa M. Soc. **29**:240, 1939.

9. Reifenstein, G. H.; Levine, S. A., and Gross, R. E.: Coarctation of the Aorta: A Review of 104 Autopsied Cases of the "Adult Type," 2 Years of Age or Older, Am. Heart J. **33**:146, 1947.

10. Edwards, J. E.; Christensen, N. A.; Clagett, O. T., and McDonald, J. R.: Pathologic Considerations in Coarctation of the Aorta, Proc. Staff Meet., Mayo Clin. **23**:324 (July 21) 1948.

showed fibrous intimal thickening and avascularity with distortion of the media. The previously reported cases of this type with pertinent data are given in the table.

REPORT OF CASE

History.—W. P., a Negro man aged 23, was admitted to the service of Dr. Russell S. Boles on July 12, 1948, with the chief complaint of pain in the back and shortness of breath of 12 days' duration. At that time he was awakened from sleep at 3 a.m. by a pain in his back just below the interscapular region. The pain was so severe that he had difficulty in taking a full respiration; the pain radiated through the chest to the sternum and was relieved somewhat in the supine position. The pain was severer at night and eased somewhat during the day. Because of its unremitting character and increase in severity, he was admitted to the hospital.

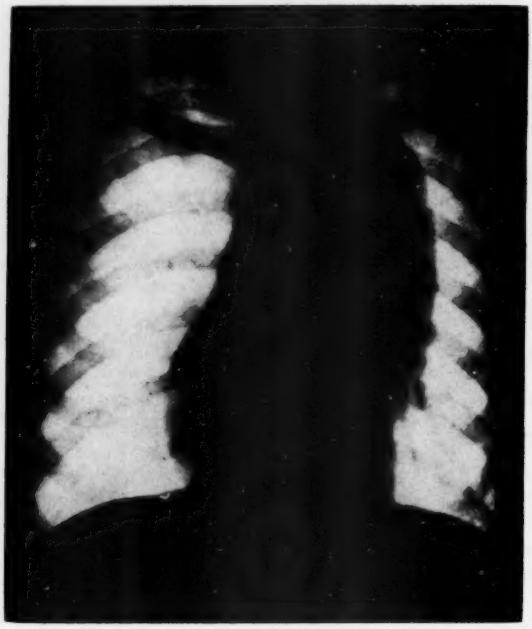

Fig. 1.—There is considerable widening and increased density of descending aorta from its origin to the diaphragm. Fluoroscopically there was no pulsation in this portion of aorta. Note condensation of lower margins and wormy erosion of the third, fourth, fifth, and sixth ribs.

The past history was irrelevant. He had served more than three years in the Army and had been discharged in 1946, apparently with normal physical findings.

Examination revealed a well-developed, well-nourished Negro man lying quietly in bed. The respirations were shallow, at a rate of 36 per minute. The heart was normal in size; the rhythm was regular. There was a harsh, rasping, Grade 3 systolic murmur present over the entire precordium, being somewhat more intense in the second left intercostal space. No murmur was heard in the back. The blood pressure in the right arm was 140/80, left arm, 136/80, right leg, 160/90, and left leg, 144/80. No congestive phenomena were present.

A roentgenogram (Fig. 1) showed the lungs to be clear; both diaphragms were clearly outlined. The heart was normal in size. There were considerable widening and increased density of the thoracic portion of the descending aorta. On fluoroscopic examination there was no pulsation in this portion of the descending aorta, although the pulsations along the heart

borders were normal. The inferior surfaces of the third, fourth, fifth, and sixth ribs revealed a slight condensation of the lower margins, with a suggestive serpentine erosion which could have been due to coarctation of the aorta. The dorsal vertebrae were normal. The trachea and esophagus were slightly displaced anteriorly. The electrocardiogram was normal.

The clinical impression was coarctation of the aorta, with dissecting aneurysm of the upper descending aorta.

The pain in the back continued, and, in addition, on the third day following admission, numbness of the left arm developed. At this time no pulses or blood-pressure reading could be obtained in the lower extremities. There was no change in size of the aneurysm on roentgen examination at this time. On July 26, a pulsating mass was observed in the left supraclavicular fossa and venous engorgement of the left arm and the left side of the neck appeared. No murmur or bruit was heard over the mass. The venous pressure was at this time 126 mm.

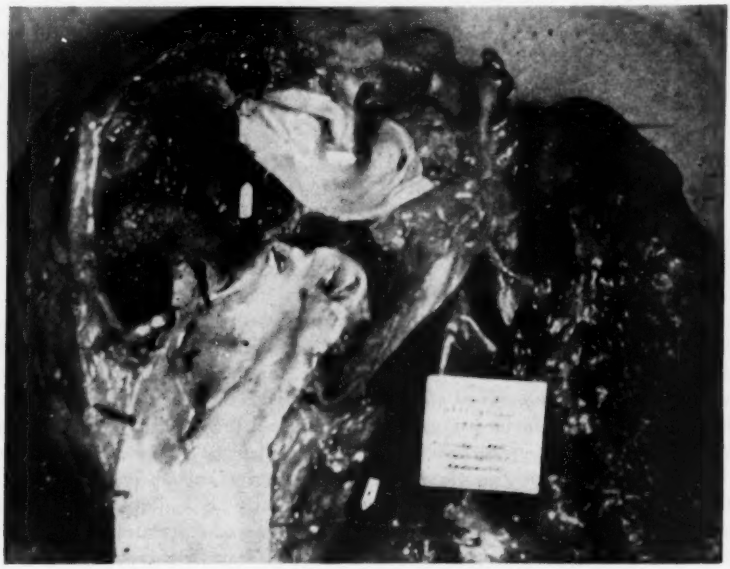

Fig. 2.—Arrow on left points to point of rupture into right lung. Uppermost arrow points to diaphragm-like septum which constricted lumen of aorta and produced coarctation. Separation between two portions of descending aorta marked point of complete transverse rupture of aorta. Arrow on the right pointing downward is in false aneurysm.

of water in the right arm and 212 mm. of water in the left arm. A roentgenogram showed increasing dilatation of the descending portion of the thoracic aorta. An angiocardiogram (Aug. 9) showed the opaque medium passing normally through the right heart, the pulmonary system, and the left heart; however, the descending aorta could not be visualized. On Aug. 14 the patient began to expectorate bright red blood, and moist rales were present at the bases of both lungs. On Aug. 16 the patient expectorated 250 cc. of bright red blood and died.

Results of Necropsy Examination.—The heart weighed 230 gm. It was small and fairly firm in consistency, and the epicardial and endocardial surfaces were clear. The valves were smooth and thin and showed nothing abnormal. The coronary vessels were widely patent throughout; the myocardium on section was bright red. No infarcts, areas of fibrosis, or other intrinsic lesions were evident.

The ascending aorta showed no pathologic changes; its wall was normal, and its intimal surface was smooth. One and five-tenths centimeters distal to the origin of the left subclavian artery the lumen of the aorta narrowed to a diameter of 6 mm. because of a diaphragm-like septum (Fig. 2). The aortic wall below the constriction was hypoplastic and was about half the thickness of the ascending aorta. Three centimeters distal to the constriction there was a small area of intimal roughening, and at this point there was a complete transverse rupture with the two segments of the aorta separated 1 cm. To the left of the aorta, at the site of rupture and communicating with its lumen, was a large aneurysmal sac which measured 6 cm. in diameter and extended into the mediastinum and the left lung. The entire posterior mediastinum was filled with clotted blood, and numerous defects in the wall of the aneurysmal sac were noted. One of these defects led to the middle portion of the left lung. The inferior boundary of the aneurysm extended slightly below the diaphragm but was well walled off.

The right pleural cavity contained approximately 1,900 cc. of freshly clotted blood; the left pleural cavity contained 200 cc. of blood-tinged clear fluid.

Microscopically there was hypoplasia of the aorta distal to the coarctation, and perivascular chronic inflammatory infiltration was noted in the thickened adventitia. Almost the entire "jet lesion" was involved in the rupture of the aorta and thus could not be studied microscopically.

COMMENT

The occurrence of rupture of the aorta distal to the point of coarctation is a relatively uncommon complication of coarctation of the aorta. In the previously reported cases and including our own, the age incidence of rupture at this site (Table) was as follows: Two occurred in the second decade, three in the third, two in the fourth, two in the fifth, and one in the seventh. The age incidence could not be obtained in two of the reported cases. The pathogenesis of this lesion is believed to be the result of the continuous trauma of jets of blood ejected through the narrowed lumen of the coarctation with increased velocity. The "jet lesion" will not be produced if the narrowed orifice is directly parallel with the center of the aortic lumen. Unfortunately, as in this case, the narrow isthmus was situated at an angle with the longitudinal axis of the aorta, with the result that the increased velocity of the blood stream was continually directed in the form of a jet upon a small localized segment of the hypoplastic aortic wall situated 3 cm. below the constriction. It is not surprising, therefore, that a localized portion of the aortic wall subjected to the constant trauma of the jet of blood may be the initiating focal point for aneurysmal formation and/or rupture. Edwards and associates [10] stressed the importance of recognizing such a lesion at operation, because if incorporated in the suture line of the surgical anastomosis it would prevent adequate healing.

SUMMARY

A rather uncommon complication of coarctation, namely, the occurrence of a "jet lesion" resulting in rupture of the aorta 3 cm. distal to the coarctation, is reported.

The pathogenic role of this lesion in producing weakening and rupture of the aortic wall is discussed.

A short review of the previously reported cases is presented.

Progress in Internal Medicine

PRESENT CONCEPTS AND RECENT ADVANCES IN ACUTE POLIOMYELITIS

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THIS REVIEW is primarily concerned with the present concepts and recent additions to knowledge of the pathogenesis and epidemiology of poliomyelitis. These can be termed the biological aspects of poliomyelitis, and in this field a number of experimental laboratories have been extremely busy during the past few years. Eventually the new facts should find more clinical application than can be assigned to them now, for one must still admit that there are no more immediate measures available for the prevention and cure of the acute disease than existed in the times of Medin and Wickman, 80 and 40 years ago, respectively.

THE POLIOMYELITIS VIRUS

Of primary importance in work on the poliomyelitis virus is the discovery by Enders and his associates, at the Children's Hospital in Boston, that poliomyelitis viruses can be propagated in non-nervous-tissue culture.[1] This is a new concept for those who have held that poliomyelitis virus is purely neurotropic. There is some danger in assuming that the "non-neurotropic" behavior of the virus in vitro indicates comparable behavior in vivo, a danger which has received recent comment [2]; nonetheless, an extraneural phase of activity for poliomyelitis virus in the clinical disease seems due for a period of renewed consideration. The concept of a systemic phase in the human disease is not new and was emphasized by Draper in 1917.[3] It has perhaps been overshadowed by later conclusions, drawn largely from experimental work, that poliomyelitis virus is essentially, if not purely, neurotropic. It is now generally accepted that poliomyelitis virus has a strong predilection for nervous tissue; that it produces its severest lesions there; that it travels easily in this tissue within the human body, but this agreement does not preclude the possibility that the virus exists extraneurally in muscles, lymph nodes, or blood, or that it acts in such extraneural sites as an antigen for the stimulation of antibodies, irrespective of its ability to produce extraneural lesions. Wenner's recent confirmation [4] of an old observation that poliomyelitis virus may be isolated from lymph nodes in fatal human cases of poliomyelitis is a reminder of the extraneural location of the virus.

From the Section of Preventive Medicine, Yale University School of Medicine.

1. Enders, J. F.; Weller, T. H., and Robbins, F. C.: Cultivation of the Lansing Strain of Poliomyelitis Virus in Cultures of Various Human Embryonic Tissues, Science **109**:85, 1949, and subsequent papers on this subject by Enders and his colleagues.

2. Faber, H. K.: The Question of Extraneural Growth in Vivo of Poliomyelitis Virus, Science **114**:570, 1951.

3. Draper, G.: Acute Poliomyelitis, Philadelphia, P. Blakiston's Son & Company, 1917; see Chap. 6.

4. Wenner, H. A., and Rabe, E. F.: The Recovery of Virus from Regional Lymph Nodes of Fatal Human Cases of Poliomyelitis, Am. J. M. Sc. **222**:292, 1951.

The question whether lesions are produced within the muscles during the acute phase of human poliomyelitis has also been considered for some time and was the subject of considerable discussion at the Second International Poliomyelitis Conference, held in Copenhagen, Sept. 3 to 7, 1951.[5] But what is more important and better proved is the fact that there may be a short phase of viremia during the incubation period of the human disease. This phase is extremely difficult to demonstrate in patients, but it has been demonstrated,[6] and experimentally it has been repeatedly shown in Horstmann's investigations on cynomolgus monkeys and chimpanzees which were infected by oral administration of virus.[7] In confirmation Bodian has also demonstrated viremia in experimental poliomyelitis in the chimpanzee.[8] Peripheral or humoral activity of the virus early in the human disease, or during what has been called the incubation period, seems to furnish a reasonable explanation for the early appearance of antibodies in clinical poliomyelitis. As is well known, by the time the major illness or "second phase" of acute poliomyelitis in the average patient is diagnosed and the patient admitted to a hospital, it is late in the clinical disease. The stage is already passed in which one might hope that either antiserum or antibiotic therapy could be effective. Within this new "extraneural concept" of the virus' activities lie the seeds of new knowledge and a new philosophy about the clinical disease.

Tissue-culture experiments indicate further that this method will eliminate the need for the use of the monkey in at least some of the large-scale experiments on virus isolation, neutralization, and typing which in the past have been so cumbersome and expensive. Enders and his associates [1] have shown that it is possible to isolate the virus in vitro from feces, as well as from other sources, to carry out neutralization tests, and even to type the virus in vitro. This lead has been quickly followed up by the work of Salk and associates [9] and Riordan, Ledinko, and Melnick.[10] It appears further that, by successive transfers of a given strain of virus in

5. Bowden, R. E. M.: A Review of Some Recent Studies of Skeletal Muscle in Anterior Poliomyelitis and Other Neuromuscular Disorders in Man and the Experimental Animal, read before the Second International Poliomyelitis Conference, Copenhagen, Sept. 3-7, 1951, to be published. See also discussion on Bowden's paper.

6. Ward, R.; Horstmann, D. M., and Melnick, J. L.: The Isolation of Poliomyelitis Virus from Human Extra-Neural Sources: IV. Search for the Virus in the Blood of Patients, J. Clin. Invest. **25**:284, 1946.

7. Horstmann, D. M., in discussion on Symposium IV: Immunity and Resistance in Poliomyelitis and Other Virus Infections, Second International Conference on Poliomyelitis, Copenhagen, Sept. 3-7, 1951, to be published; cited by Paul, J. R.: Current Knowledge and Trends in Poliomyelitis, Merck Rep. **61**:3, 1952. Horstmann, D. M.: Poliomyelitis in the Blood of Orally Infected Monkeys and Chimpanzees, Federation Proc. **11**:471, 1952; Proc. Soc. Exper. Biol. & Med. **79**:417, 1952.

8. Bodian, D.: Pathogenesis of Poliomyelitis in Normal and Passively Immunized Primates After Virus Feeding, Federation Proc. **11**:462, 1952; A Reconsideration of the Pathogenesis of Poliomyelitis, Am. J. Hyg. **55**:414, 1952.

9. Youngner, J. S.; Ward, E. N., and Salk, J. E.: Studies on Poliomyelitis Viruses in Cultures of Monkey Testicular Tissue: I. Propagation of Virus in Roller Tubes, Am. J. Hyg. **55**:291, 1952.

10. Riordan, J. T.; Ledinko, N., and Melnick, J. L.: Multiplication of Poliomyelitis Viruses in Tissue Cultures of Monkey Testes: II. Direct Isolation and Typing of Strains from Human Stools and Spinal Cords in Roller Tubes, Am. J. Hyg. **55**:339, 1952. Ledinko, N.; Riordan, J. T., and Melnick, J. L.: Multiplication of Poliomyelitis Viruses in Tissue Cultures of Monkey Testes: I. Growth Curves of Type I (Brunhilde) and Type II (Lansing) Strains and Description of a Quantitive Neutralization Test, ibid. **55**:323, 1952.

tissue culture, there may be an attenuation of the virus in its capacity to paralyze monkeys. It does not require a seer to predict that within this type of experiment lies another approach to the possible production of nonvirulent strains, which could have great practical value.

In these recent discoveries it is possible that we have witnessed the end of what might be termed "the monkey era" in poliomyelitis research. This is no great loss, for the expense of maintaining monkey colonies for poliomyelitis research has been great. Also it is heartening to realize that the way is now open for many laboratories to engage in certain clinical and epidemiological investigations on poliomyelitis which have been denied to them in the past because of expense and other difficulties. Scores of new investigators can now enter the poliomyelitis field, and new impetus can be given to such work all over the world. All this stems from the discovery that a tissue-culture tube may be substituted for a monkey.

One of the most practical outcomes of the poliomyelitis-virus tissue-culture technique is the fact that all three known strains of the virus may eventually be grown and concentrated from tissue-culture fluid to the extent that they can serve as a compliment-fixing antigen.[11] For some 35 years, research workers have tried to develop a test for the diagnosis of recent poliomyelitis infection. During all that time the absence of such a test in poliomyelitis has seriously hampered progress in the clinical diagnosis.[12] It may not be too soon to predict that we have witnessed the end of another era, namely, that in which poliomyelitis has been diagnosed by clinical examination and spinal fluid determinations alone. Hereafter, these clinical examinations may be gradually supplemented by serologic methods, the approach which has proved to be of so much value in the diagnosis of other neurotropic virus infections.

In regard to new facts about the virus itself, it is to be recalled that poliomyelitis virus is a fastidious organism with a limited animal host range. It is extremely small as viruses go and has not yet been clearly visualized in the electron microscope. It is labile in some respects, being highly sensitive to drying, yet quite resistant to some chemicals and belongs to the ether-resistant group, a category recently established by Andrewes and Horstmann.[13] Its place, taxonomically speaking, among other viruses turns out to be a matter of some controversy,[14] but there is a backlog of opinion that poliomyelitis viruses logically belong to a special family or genus to be separated from encephalomyelitic viruses, and particularly from the Coxsackie viruses.[15]

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11. Svedmyr, A.; Enders, J. F., and Holloway, A.: Complement Fixation with Brunhilde and Lansing Poliomyelitis Viruses Propagated in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **79**:296, 1952.

12. Casals and Olitsky (A Complement-Fixation Test for Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **75**:315, 1950), using infected baby mouse brains as an antigen, had previously developed a single-type complement-fixation test useful for the diagnosis of Lansing (Type 2) poliomyelitis virus infection. It has valuable but limited clinical application.

13. Andrewes, C. H., and Horstmann, D. M.: The Ether Sensitivity of Viruses, J. Gen. Microbiol. **3**:290, 1949.

14. Committee on Nomenclature of the National Foundation for Infantile Paralysis: A Proposed Provisional Definition of Poliomyelitis Virus, Science **108**:701, 1948.

15. Rhodes, A. J.: Poliomyelitis Virus Group: I; Koprowski, H.: Poliomyelitis Virus Group: II, read at the Conference on Virus and Rickettsial Classification and Nomenclature, New York Academy of Science, January, 1952.

Within the poliomyelitis family there are three, perhaps four, species (or subspecies) designated as immunologic types; these include the so-called Lansing, Brunhilde, and Leon types. It has been shown repeatedly in the laboratory (particularly in work on feeding chimpanzees) that, although type-specific immunity exists, an animal can be reinfected repeatedly with heterologous types of poliomyelitis virus. This, by the way, is the reason usually given to try to explain why the same individaul may contract poliomyelitis more than once; that is, the repeated reinfection is an example of infection by multiple types. The practical question arises, of course, whether the average adult becomes immune to all three or more types, and whether, if a vaccine is to be produced, the average child should be immunized to all three types before he or she can properly be considered to be immune to poliomyelitis. Such questions remain to be answered.

The biological or clinical significance of the types of poliomyelitis virus has a number of implications. Salk, of the University of Pittsburgh, has been the chairman of a committee responsible for an immense program sponsored by The National Foundation for Infantile Paralysis for the typing of poliomyelitis strains, the determination of their relative frequencies, and the establishment of their geographical distribution.[16] More significant here than the mere classification into three or four types has been an analysis of epidemiological and clinical circumstances in which these different types of poliomyelitis virus are found. It appears that different types of poliomyelitis virus may give rise to different clinical pictures, with relative potentialities to paralyze on the one hand and to immunize on the other. During poliomyelitis epidemics, far and away the greatest number of strains obtained from clinical (nonfatal) cases have been of the Brunhilde type, whereas strains of the Lansing type have been largely isolated from scattered fatal cases. Actually, the Lansing strain appears to produce relatively less paralytic poliomyelitis per individual infected than do other strains. No epidemic of the Lansing strain of poliomyelitis (confirmed by strain isolation) has been described firsthand. Yet the Lansing virus is apparently common in many locations, as the antibody surveys by Sabin,[17] Hammon and associates,[18] and the Yale Poliomyelitis Study Unit [19] have shown. These surveys have been concerned with the presence and frequency of Lansing antibodies in different populations at different times, and from them one can map out the past history of poliomyelitis within a given population by measuring the presence of serum-neutralizing antibodies in the different age groups. From such studies in serologic epidemiology with the Lansing strain of poliomyelitis virus, it now appears that (*a*) the average age at which clinical poliomyelitis is usually acquired in a given population and (*b*) the average age at which Lansing anti-

16. Committee on Typing of the National Foundation for Infantile Paralysis: Immunologic Classification of Poliomyelitis Viruses: I., Am. J. Hyg. **54**:191, 1951.

17. Sabin, A. B.: The Epidemiology of Poliomyelitis at Home and Among the Armed Forces Abroad, J. A. M. A. **134**:749, 1947.

18. Hammon, W. M.: Immunity in Poliomyelitis, Bact. Rev. **13**:135, 1949. Hammon, W. M.; Sather, G. E., and Hollinger, N.: Preliminary Report of Epidemiological Studies on Poliomyelitis and Streptococcal Infections, Am. J. Pub. Health **40**:293, 1950.

19. Paul, J. R.; Melnick, J. L., and Riordan, J. T.: Comparative Neutralizing Antibody Patterns to Lansing (Type 2) Poliomyelitis Virus in Different Populations, to be published.

bodies are acquired often are the same. This has been shown by Gear in his survey in South Africa,[20] by Paul and co-workers in studies on sera from Cairo, Egypt,[21] and by other investigators elsewhere.

From such surveys it also appears that in certain tropical areas where poliomyelitis had previously been thought to be rare, as determined by case reporting, it is not rare. Actually it is common, if incidence is determined on the basis of the early development of Lansing antibodies, even among infants 1 or 2 years of age, who, one assumes, develop these antibodies in the course of a subclinical infection. This has been found by Hammon on the island of Guam and elsewhere [18] and by Paul and colleagues in Cairo.[21] In such areas more than half of the locally born native infants had acquired Lansing antibodies by the age of 14 months, and throughout subsequent life the level was maintained at about 100%. The speedy acquisition of Lansing antibodies in infancy within these tropical areas suggests that infants there are heavily exposed to and infected by an agent which has the capacity to give rise to this antibody and that this agent must be very widespread locally. Gear's explanation is that, with so much exposure and immunization continually occurring in early life, the number of susceptible persons may seldom become large enough to give rise to an epidemic.[22]

Another important epidemiological observation of clinical significance is that with division of an urban population, in this country for instance, into two groups, *a* and *b*, *a* representing the upper socioeconomic stratum who live under moderately good conditions and *b*, the lower stratum who have poor living conditions, antibodies to the Lansing strain of poliomyelitis virus appear at an earlier age among *b*, the lower-stratum children, than among *a*, the upper-stratum children. This has been shown from the studies of Hammon and colleagues [18] and Melnick and Ledinko.[23] Along this same line of thought, we have witnessed a change in the age distribution of poliomyelitis during the past two generations. In our grandparents' time poliomyelitis was a disease of infants—the true, "old-fashioned" infantile paralysis. Indeed, according to physicians in New York City, at the turn of the century the malady was rarely seen in children more than 6 years of age. Today, we find, not only in the northern half of this continent but also more particularly in Scandinavia, the rest of Europe, and Australia, that poliomyelitis is not limited to infants but is more commonly seen in children of school and teen age. Since 1945, perhaps 25% of patients in New England are 15 years of age or more.[24] This change in the age level of incidence has not taken place everywhere, for the disease is still concentrated among infants in certain primitive and tropical countries. Hence one might suppose that the alteration in the age incidence of the disease is somehow associated with the conditions of our 20th-century way of life, such as the changing character and composition of our population and the curtailment in the size of

20. Gear, J. H. S.; Measroch, V., and Bradley, J.: Poliomyelitis in South Africa: Studies in an Urban Native Township During a Non-Epidemic Year, South African M. J. **25**:297, 1951.

21. Paul, J. R.; Melnick, J. L.; Barnett, V. H., and Goldblum, N.: A Survey of Neutralizing Antibodies to Poliomyelitis Virus in Cairo, Egypt, Am. J. Hyg. **55**:402, 1952.

22. Gear, J. H. S.: Extrahuman Sources of Poliomyelitis, read before the Second International Poliomyelitis Conference, Copenhagen, Sept. 3-7, 1951, to be published.

23. Melnick, J. L., and Ledinko, N.: Social Serology: Antibody Levels in a Normal Young Population During an Epidemic of Poliomyelitis, Am. J. Hyg. **54**:354, 1951.

24. In 1951 in Connecticut, 35% of the poliomyelitis patients were 15 years of age or older.

families. Perhaps highly modern "hygienic methods" have reached the point at which infants and young children are more protected from exposure to this virus today than they were in our grandparents' time. But modern "hygiene" has not reached the point of providing protection later in life (that is, during childhood or adolescence), so that the occasional clinical attack of poliomyelitis has been postponed, not eliminated. As a clinical attack of poliomyelitis is apt to be severer in older patients (more than 15 years of age), it becomes questionable whether the present state of affairs is wholly desirable.

CLINICAL ASPECTS OF POLIOMYELITIS

It appears that one sees more cases in adults now than previously, and since age seems to condition the clinical picture somewhat,[25] one should appreciate what the adult picture is. In the adult form of the disease, one does not see so often the dromedary form characterized by two distinct bouts of fever and illustrative of the minor and the major illnesses of poliomyelitis. In adult poliomyelitis the onset is apt to be more insidious,[26] the duration of the acute stage is more prolonged, pain in the limbs and back is more pronounced, and the outcome is severer than in the average infantile case. The last feature is true of many acute virus diseases, such as measles, mumps, and infectious hepatitis, which are severer in adult life than in childhood.

Mention should be made of other observations with clinical significance, namely, that the elements of trauma, stress, surgical operations, and even injections have been regarded with increasing seriousness as so-called precipitating factors in paralytic poliomyelitis. For more than 75 years the observation has been recorded in medical literature that injury, exertion, stress, or strain experienced by a given patient in the early stages of acute poliomyelitis seemed to act unfavorably on the subsequent clinical course of the disease, but little was made of it. Studies by Russell, of Oxford University, England,[27] and by Horstmann in this country [28] indicate that if severe exertion and stress are experienced a day or two immediately following the onset of poliomyelitis the prognosis is less favorable than it would be if this had not happened. While there is not complete agreement on this point in infantile or juvenile cases,[29] the evidence is strong in adult cases. Two explanations have been suggested. One is that the metabolic changes which may occur in nerve cells as a result of severe physical exertion favor the parasite over the host and make it easier for the virus, already present, to multiply and spread; another is that the release of certain adrenal cortical hormones, occurring as a "stress reaction" in exertion, gives rise to a similar severe result. In this connection there is the possible unfavorable effect of a long ambulance ride to the hospital,[30] the

25. Horstmann, D. M.: Clinical Aspects of Acute Poliomyelitis, Am. J. Med. **6**:592, 1949.

26. Paul, J. R.: Poliomyelitis: Early Diagnosis and Early Management of Acute Cases, Ann. Int. Med. **30**:1126, 1949.

27. Russell, W. R.: Poliomyelitis: Pre-Paralytic Stage and the Effect of Physical Activity on the Severity of Paralysis, Brit. M. J. **2**:1023, 1947.

28. Horstmann, D. M.: Acute Poliomyelitis: Relation of Physical Activity at Time of Onset to Course of Disease, J. A. M. A. **142**:236, 1950.

29. Albrecht, R. M., and Locke, F. B.: Effect of Physical Activity on Prognosis of Poliomyelitis, J. A. M. A. **146**:769, 1951.

30. Brahdy, M. B.: Effect of Transportation on Severity of Acute Poliomyelitis, J. A. M. A. **146**:772, 1951.

multiple physical examinations, the muscle testing, the needles, the lumbar punctures, etc. All this adds up to the hypothesis that mildly ill nonparalytic poliomyelitis patients may well be kept at home, regardless of whether welfare agencies stand ready to foot the hospital bill. More and more it appears that physicians throughout the country are coming around to this point of view.

In this connection, there has been an accumulating mass of evidence to indicate that operations about the mouth, for example, tonsillectomy or tooth extraction, if performed within three months of the onset of the disease, increase the likelihood not only of acquiring the paralytic form of infection but also of acquiring the severe bulbar form.[31]

Of more recent origin is the evidence that even diphtheria or pertussis immunization, if given within a few weeks prior to the onset of acute poliomyelitis, may increase the chances of acquiring paralysis and may result in paralysis of the limb into which the injections were given. These indications originally came in 1950 from England and Australia,[32] but surveys made in this country [33] are now beginning to appear which also show that in a small fraction of cases an injection of antigen or a "preillness immunization" exerts some unfavorable effects. However, although this finding has important public health implications, the percentage of such cases in a given epidemic of poliomyelitis is so small that the problem is not one of great magnitude. What should be done about it is a matter to be settled by national, state, or municipal health officers. It seems logical to postpone inoculations during epidemic times, just as one postpones elective surgery under the same conditions, but in the absence of a poliomyelitis epidemic it seems illogical to magnify the ill-effects of inoculations in a manner which might interfere with the immunization program for other important diseases. A statement to this effect has recently appeared.[34]

PROGRESS IN PREVENTION OF POLIOMYELITIS

Next is a report of the progress (or the lack of it) in the prevention of poliomyelitis. Methods for controlling the spread of this disease should logically follow two lines: (1) the attempt to eliminate the virus from a community by so-called sanitary or quarantine measures, as, for instance, used to be applied when cholera appeared in this country, and (2) the attempt to bolster human resistance by immunization, as one does in vaccination against smallpox.

Concerning the first approach, there is agreement among students of poliomyelitis that not enough is known about the factors responsible for the spread of

31. Anderson, G. W.; Anderson, G.; Skaar, A. E., and Sandler, F.: Risk of Poliomyelitis After Tonsillectomy, Ann. Otol. Rhin. & Laryng. **59**:602, 1950.

32. McCloskey, B. P.: The Relation of Prophylactic Inoculations to the Onset of Poliomyelitis, Lancet **1**:659, 1950. Hill, A. B., and Knowelden, J.: Inoculation and Poliomyelitis, Brit. M. J. **2**:1, 1950.

33. Anderson, G. W., and Skaar, A. E.: Poliomyelitis Occurring After Antigen Injections, Pediatrics **7**:741, 1951. Greenberg, M.; Abramson, H.; Cooper, H. M., and Solomon, H. D.: The Relation Between Recent Injections and Paralytic Poliomyelitis in Children, Am. J. Pub. Health **42**:142, 1952. Korns, R. F.; Albrecht, R. M., and Locke, F. B.: The Association of Parenteral Injections with Poliomyelitis, ibid. **42**:153, 1952.

34. Relationship Between Inoculations and Poliomyelitis, editorial, J. A. M. A. **149**:170, 1952.

poliomyelitis to enable elimination of the virus from a community. Thus, although it is agreed that poliomyelitis is a disease generally spread by personal contact, the situation is more complex than that, for in most parts of the world the prevalence of poliomyelitis is influenced or even dominated in a mysterious manner by season and climate. No satisfactory reason has as yet been proposed to explain the occurrence of epidemics of poliomyelitis in the temperate zones of the world at so much higher a rate in the summer than in the winter. There are two possible explanations: either something happens in the summer which enormously facilitates the spread and dissemination of the virus throughout a community, or something happens which makes some persons, the nonimmune persons, enormously more vulnerable and far more apt to acquire the disease in summer than at other times of the year.

A further difficulty which might block attempts to eliminate the virus from a community is the fact that there is little exact knowledge that an extrahuman reservoir of virus is epidemiologically important; in other words, it is not known whether the disease may be spread by agents other than infected persons, as, for instance, by insects or contaminated food or water. Theoretically these agents might be "eliminated" by the introduction of "improved sanitary measures." One recognizes that food or flies [35] or cockroaches [36] could on occasion be infectious, but no evidence exists that such insects are an essential link in the chain, comparable with mosquitoes when they carry the parasite of malaria or the virus of yellow fever.

Furthermore, other, larger and probably inaccessible human "reservoirs" of infection exist, for both during overt epidemics and at other times potentially infectious individuals, representing the abortive cases, are at large in a community and there is no way of labeling them as such or of controlling their activities. Thus, the present outlook for elimination of the virus from a community by sanitary measures, coupled with the control of human activity through quarantine measures, is not hopeful. Nevertheless, the recent indication that during certain outbreaks the virus is concentrated around the known or recognized cases [37] should be a guide to situations in which such measures might be more effective.

Actually, the attempt to render the local environment "virus free" may not seem to be the best solution to the problem of control of poliomyelitis, although it should not be forgotten.

A second approach to the prevention of poliomyelitis is that of active (or passive) immunization. What is obviously needed in the struggle to prevent poliomyelitis is some means of bolstering the immunity of children (and adults) to enable them to resist the infection induced by periodic exposure to the virus; that is, one might combat poliomyelitis as one combats smallpox, diphtheria, and whooping cough, by vaccination. Since no vaccine for poliomyelitis is as yet available, predictions are in the realm of speculation. However, there are two or three lines to be followed: (1) the use of inactivated virus, so-called killed virus (with or with-

35. Ward, R.; Melnick, J. L., and Horstmann, D. M.: Poliomyelitis Virus in Fly-Contaminated Food Collected at an Epidemic, Science **101**:491, 1945.

36. Syverton, J. T.; Fischer, R. G.; Smith, S. A.; Dow, R. P., and Schoof, H. F.: The Cockroach as a Natural Extrahuman Source of Poliomyelitis, Federation Proc. **11**:483, 1952.

37. Brown, G. C.; Ainslie, J. D.; Gilliam, A. G.; Zintek, A. R., and Francis, T.: Studies on the Distribution of Poliomyelitis Virus: VI. In a Small Community in an Epidemic Area, Am. J. Hyg. **55**:49, 1952.

out adjuvants), which would yield a vaccine comparable with those used in rabies or influenza; or (2) the administration of a live vaccine in which one would hope to use a modified or attenuated virus, comparable perhaps with the method used against smallpox or that used in vaccination against yellow fever. These are questions with which many laboratories are involved. It seems unlikely, however, that an effective vaccine will be attained by investigators working on mice and monkeys alone, for the real experiment will come when the new hypothetical "vaccines" are tried on man. Such experiments will require judgment and courage, as well as technical ability.

A third type of "immunization" is the use of immune sera in the form of gamma globulin as a means of inducing passive immunity during an epidemic in order to tide persons over the epidemic period. The material might have to be given several times during an epidemic. Possibly during the transient period of protection artificially produced in this way, the protected person could happily be exposed and conceivably develop so-called passive-active immunity, as in the production of modified measles. This would be a useful plan but one difficult to effect. A trial of this procedure was carried out by Hammon, of the School of Public Health, University of Pittsburgh, during an epidemic in Utah last (1951) summer.[38] Results have not yet been published. It is probable that more trials will be necessary before the value of the procedure is known.

SUMMARY

In attempting to summarize the advances or changes in point of view which have taken place in the poliomyelitis field over the past decade, one is struck by the reversals of the opinions held in the 1930's. Whether these reversals are due to an actual evolution in the behavior of the disease or to an evolution in the thinking of the persons who have worked on the disease is not clear. But a disease originally regarded as being limited to infants is now no longer confined to infancy. A disease originally considered mildly contagious is now regarded as very contagious, almost as much so as measles. A disease whose clinical picture was originally thought to be limited to acute paralysis is now regarded as a disease in which only one in a hundred or more of those infected become paralyzed, and if the Lansing strain is involved perhaps one in a thousand, all the others having the nonparalytic, abortive, or inapparent infections. Originally thought to be rare in the tropics, it now appears to be commoner and more endemic there than elsewhere. In other areas, from an endemic disease it has tended to become epidemic; from a curiosity it has become a common, periodic scourge; and, incidentally, an item of great public interest—too great perhaps, one is sometimes inclined to think. To recapitulate: In all probability, poliomyelitis, like many other diseases, is changing over the years; at the same time, new laboratory tools and new ideas have been introduced which now indicate that some of the oldest theories are, or rather were, correct.

38. Hammon, W. M.: Read before the Meeting of the American Epidemiological Society, Pittsburgh, April, 1952.

Books

Office Endocrinology. By Robert B. Greenblatt, M.D. Fourth edition. With a foreword by G. L. Kelly. Price, $10.50. Pp. 561, with 276 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

This book has many areas of appeal. As stated on the cover leaf, it is not an encyclopedic textbook but touches on many of the clinical problems in endocrinology that face the general physician. The book is divided into five sections, of which those sections related to gonadal dysfunction are exceedingly well done and would be quite useful as a source of reference for many practicing physicians. However, the section on general endocrinology is exceedingly brief and in many places inadequate, as it provides much less reference material than the average recently published general textbook in medicine. The section on hormonology (a questionably appropriate heading) gives a brief résumé of the more obvious physiological activities of the various hormones, along with a rather complete list of the available pharmaceutical preparations. However, even in this section, the advisability of recommending the use of commercially available growth hormones for the production of growth in dwarfism is questioned, as there is no clinical evidence to warrant this recommendation. The section on diagnostic procedures will be quite helpful to most general physicians, and, although limited in its scope, we must not forget the original premise that this book is not intended to be encyclopedic.

In these days of tremendous accumulation of factual knowledge in this rapidly growing field of endocrinology and metabolism, it is unreasonable to expect any book to provide complete and up-to-date information on all phases of so broad a subject. Many books on endocrinology have been published recently which provide more details, more background, and more experimental evidence and are more careful in their ultimate conclusions. However, it must be said that Dr. Greenblatt has provided, in a single volume, a group of the commoner problems faced by the general physician and has provided an outline for the study of these conditions.

Signs and Symptoms. By many contributors. Edited by Cyril M. MacBryde, M.D. Second edition. Price, $10. Pp. 783, with 98 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1952.

Each of the 31 chapters of this excellent book is an essay on one major sign or symptom presented by the patient as he comes to the physician's care. Emphasis is upon pathologic physiology. Results of recent investigations have been incorporated. Each subject has been presented at a graduate level and in terms of present concepts. Particularly impressive are the discussions on pathologic bleeding, disturbances of consciousness and of muscle movement, fainting, fever, dyspnea, cyanosis, pain in its various locations, dehydration, edema, obesity, and undernutrition. The book is recommended as an up-to-date, although conservative, presentation of those fields of pathologic physiology in the problems of internal medicine that have been cultivated extensively in the past decade or two.

The format of the book is excellent. Each page is set in double columns, and most chapters have a short bibliography of important references.

The Fight Against Tuberculosis: An Autobiography. By Francis Marion Pottenger, with an introduction by Roy G. Hoskins, M.D. Price, $4. Pp. 276, with illustrations. Henry Schuman, Inc., Publishers, 20 E. 70th St., New York 21, 1952.

The qualities which make biographical writing great are somewhat intangible, and just why such works as Boswell's "Johnson," Lockhart's "Life of Scott," Trevelyan's "Life of Macauley," and E. L. Trudeau's biography are satisfying is hard to define. Be this as it may, Dr. Pottenger's autobiography is interesting, and indeed often exciting, from start to finish. Written in precise and vivid style, one sees with the author the scenes of his childhood and feels with him the struggles and trials he went through in getting his medical education and finally establishing his sanatorium in Monrovia. Those of us who know and are fond of Frank Pottenger will understand him better after reading this charming story of his life, in which his personal characteristics are well summed up—eagerness, intense interest in life, kindness, and honesty.

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Peritrate® tetranitrate
(brand of pentaerythritol tetranitrate)

a longer-lasting oral coronary dilator for prophylactic management of angina pectoris

Extensive clinical trials[1-3] demonstrate that Peritrate Tetranitrate may be used effectively in certain cases

1. to reduce the number of anginal attacks
2. to reduce the severity of attacks not prevented.

Of cases reported in one study, 78.4% obtained reduction in the number of attacks. In some less responsive patients, "attacks not prevented were less intense and of shorter duration."[1]

Increased exercise tolerance: In patients studied to determine Peritrate's effect on precordial pain produced by exercise, improvement was noted in every case. An increase of 50-75% in distance walked was not unusual.[1]

EKG evidence: When anginal attacks are induced by exercise, shifts in the S-T segments or inversion of the T waves are prevented or minimized.

Toxicity and Side Effects: No significant toxic manifestations have been observed in patients so far studied. Side effects, such as occasional headache or nausea, are infrequently seen and tend to disappear after a few days of the medication.

Literature and samples on request.

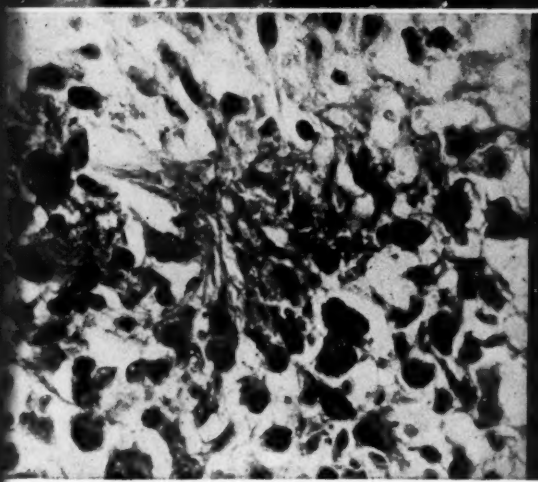
1. *Angiology 3:1 (Feb.) 1952.*
2. *Angiology 3:16 (Feb.) 1952.*
3. *Angiology 3:20 (Feb.) 1952.*

CHILCOTT *Laboratories, INC.* MORRIS PLAINS, NEW JERSEY
FORMERLY THE MALTINE COMPANY

response in rheumatic fever

q. Does cortisone influence the heart lesions of rheumatic fever?

a. Early cortisone administration suppresses and in some cases may even prevent serious cardiac damage.



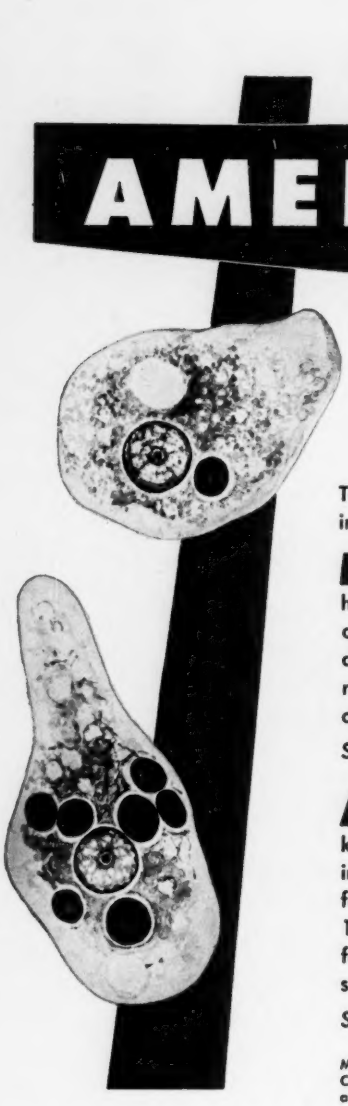
q. What effect does cortisone have on acute rheumatic fever?

a. Often within 24 hours after cortisone therapy, the severely ill, toxic patient appears alert and comfortable; and within one to four days, temperature drops to normal, appetite increases, and polyarthritis subsides.

Cortisone Upjohn

available as compressed tablets Cortisone Acetate, 25 mg., for oral use. Bottles of 20 tablets.

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN



AMEBIASIS

To combat intestinal and extra-intestinal amebiasis, found in every state of the Union:

MILIBIS® because of relative insolubility, assures high concentration in the large intestine, very effective against subacute and chronic amebiasis. Average adult dose: 0.5 Gm. (1 tablet) three times daily for 7 to 10 days, repeated if necessary. Control acute dysentery first or concurrently with emetine.

Supplied in 0.5 Gm. tablets, bottles of 25.

ARALEN® Diphosphate —the well known antimalarial—induces *complete clinical remission* in pleuropulmonary amebiasis[1] as well as hepatic and other forms of extra-intestinal amebiasis.[2,3] Average adult dose: 1 Gm. (4 tablets) daily for 2 days, then 0.5 Gm. daily for 2 to 3 weeks, which may be combined with or successive to Milibis therapy of intestinal amebiasis.

Supplied in 0.25 Gm. tablets, bottles of 100 and 1000.

Milibis and Aralen, trademarks reg. U. S. & Canada, brand of bismuth glycolylarsanilate and chloroquine, respectively.

1. Lindsay, A. E., Gossard, W. H., and Chapman, J. S.: *Dis. Chest*, 20:533, Nov., 1951.
2. Conan, N. J., Jr.: *Am. Jour. Med.*, 6:309, Mar., 1949.
3. Emmett, J.: *J.A.M.A.*, 141:22, Sept. 3, 1949.

Illustrated brochure on request.

WINTHROP-STEARNS INC.
New York 18, N. Y. Windsor, Ont.